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# **Dyslipidaemia, glucose intolerance and cardiovascular disease mortality and morbidity in Europeans and Asians**

Lei Zhang

Department of Public Health, Hjelt Institute  
University of Helsinki and  
Diabetes Prevention Unit, Department of Chronic Disease Prevention  
National Institute for Health and Welfare  
Helsinki, Finland  
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## **Supervisors**

Docent Qing Qiao, MD, PhD

Department of Public Health, Hjelt Institute, University of Helsinki and  
Diabetes Prevention Unit, Department of Chronic Disease Prevention  
National Institute for Health and Welfare, Helsinki, Finland

Professor Jaakko Tuomilehto, MD, PhD

Department of Public Health, Hjelt Institute, University of Helsinki and  
Diabetes Prevention Unit, Department of Chronic Disease Prevention  
National Institute for Health and Welfare, Helsinki, Finland

## **Reviewers**

Professor Ronald P. Stolk, MD, PhD

Department of Epidemiology, University Medical Center Groningen  
University of Groningen  
Groningen, the Netherlands

Professor Timo E. Strandberg, MD, PhD

Department of Health Sciences/Geriatrics, University of Oulu  
Unit of General Practice, Oulu University Hospital  
Oulu, Finland

## **Opponent**

Docent Jorma Lahtela, MD, PhD

Department of Medicine, University of Tampere  
Tampere, Finland

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## LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the original publications listed below. They are referred to in the text by their Roman numerals (I-V).

- I. Zhang L, Qiao Q, Tuomilehto J, Hammar N, Alberti K.G.M.M, Eliasson M, Heine R.J, Stehouwer C.D.A, Ruotolo G, for the DECODE Study Group. Blood lipid levels in relation to glucose status in European men and women without a prior history of diabetes: the DECODE Study. *Diabetes Research and Clinical Practice* 2008; 82: 364-377.
- II. Zhang L, Qiao Q, Tuomilehto J, Hammar N, Janus E.D, Söderberg S, Mohan V, Ramachandran A, Dong Y.H, Lam T.H, Pang Z.C, for the DECODA Study Group. Blood lipid levels in relation to glucose status in 7 populations of Asian origin without a prior history of diabetes: the DECODA Study. *Diabetes/Metabolism Research and Reviews* 2009; 25: 549-557.
- III. Zhang L, Qiao Q, Tuomilehto J, Janus E.D, Lam T.H., Ramachandran A, Mohan V, Stehouwer C.D.A, Dong Y.H, Nakagami T, Onat A, Söderberg S, for the DECODE/DECODA Study Group. Distinct ethnic differences in lipid profiles across glucose categories. *Journal of Clinical Endocrinology & Metabolism* 2010; 95: 1793-1801.
- IV. Zhang L, Qiao Q, Tuomilehto J, Hammar N, Ruotolo G, Stehouwer C.D.A, Heine R.J, Eliasson M, Zethelius B, for the DECODE Study Group. The impact of dyslipidaemia on cardiovascular mortality in European men and women without a prior history of diabetes in the DECODE study. *Atherosclerosis* 2009; 206: 298-302.
- V. Zhang L, Qiao Q, Laatikainen T, Söderberg S, Jousilahti P, Onat A, Nilsson P, Tuomilehto J, for the DECODE Study Group. The impact of dyslipidaemia on incidence of coronary heart disease in Finns and Swedes with different categories of glucose tolerance (Under review).

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## **ABBREVIATIONS**

ABCA1 adenosine triphosphate-binding cassette transporter A1

ApoA apolipoprotein A

ApoB apolipoprotein B

ApoC apolipoprotein C

ApoE apolipoprotein E

BMI body mass index

CETP cholesteryl ester transfer protein

CH combined fasting and post-load hyperglycaemia

CHD coronary heart disease

CI confidence interval

CVD cardiovascular disease

DECODA Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Asia

DECODE Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe

ERN extended-release niacin

FC Free cholesterol

FFA free fatty acid

FPG fasting plasma glucose

HbA1c hemoglobin A1c

HDL-C high-density lipoprotein cholesterol

HMG-CoA 3-hydroxy-3-methyl-glutaryl-CoA

HR hazard ratio

ICD International Classification of Diseases

IDL intermediate-density lipoproteins

IFG impaired fasting glucose

IGT impaired glucose tolerance

LCAT lecithin-cholesterol acyl transferase

LDL-C low-density lipoprotein cholesterol

Lp(a) Lipoprotein(a)

LPL lipoprotein lipase

MGs monoglycerides

NFG normal fasting glucose

NGT normal glucose tolerance

Non-HDL-C non-high-density lipoprotein cholesterol

OGTT oral glucose tolerance test

SBP systolic blood pressure

TC total cholesterol

TC/HDL-C total cholesterol/high-density lipoprotein cholesterol

TG triglycerides

VLDL very-low-density lipoprotein

WHO World Health Organization

2hPG 2-hour plasma glucose



## ABSTRACT

Dyslipidaemia, a major risk factor of cardiovascular disease (CVD), is prevalent not only in diabetic patients but also in individuals with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). The aims of this study were: 1) to investigate lipid levels in relation to glucose in European (I) and Asian (II) populations without a prior history of diabetes; 2) to study the ethnic difference in lipid profiles controlling for glucose levels (III); 3) to estimate the relative risk for cardiovascular mortality (IV) and morbidity (V) associated with dyslipidaemia in individuals with different glucose tolerance status.

Data of 15 European cohorts with 19 476 subjects (I and III) and 13 Asian cohorts with 19 763 individuals (II and III) from 21 countries aged 25-89 years, without a prior history of diabetes at enrollment, representing Asian Indian, Chinese, European, Japanese and Mauritian Indian, were compared. The lipid-CVD relationship was studied in 14 European cohorts of 17 763 men and women which provided with follow-up data on vital status, with 871 CVD deaths occurred during the average 10-year follow-up (IV). The impact of dyslipidaemia on incidence of coronary heart disease (CHD) in persons with different glucose categories (V) was further evaluated in 6 European studies, with 9087 individuals free of CHD at baseline and 457 developed CHD during follow-up. Z-scores of each lipid component were used in the data analysis (I, II, IV and V) to reduce the differences in methodology between studies. Analyses of cardiovascular mortality and morbidity were performed using Cox proportional hazards regression analysis adjusting for potential confounding factors.

Within each glucose category, fasting plasma glucose (FPG) levels were correlated with increasing levels of triglycerides (TG), total cholesterol (TC), TC to high-density lipoprotein (HDL) ratio and non-HDL cholesterol (non-HDL-C) ( $p < 0.05$  in most of the ethnic groups) and inversely associated with HDL-C ( $p < 0.05$  in some, but not all, of the populations). The association of lipids with 2-h plasma glucose (2hPG) followed a similar pattern as that for the FPG, except the stronger association of HDL-C with 2hPG. Compared with Central & Northern (C&N) Europeans, multivariable adjusted odd ratios (95% CIs) for having low HDL-C were 4.74 (4.19-5.37), 5.05 (3.88-6.56), 3.07 (2.15-4.40) and 2.37 (1.67-3.35) in Asian Indian men but 0.12 (0.09-0.16), 0.07 (0.04-0.13), 0.11 (0.07-0.20) and 0.16 (0.08-0.32) in Chinese men who had normoglycaemia, prediabetes, undiagnosed and diagnosed diabetes, respectively. Similar results were obtained for women. The prevalence of low HDL-C remained higher in Asian Indians than in others even in individuals with LDL-C  $< 3$  mmol/l. Dyslipidaemia was associated with increased CVD

mortality or CHD incidence in individuals with isolated fasting hyperglycaemia or IFG, but not in those with isolated post-load hyperglycaemia or IGT.

In conclusion, hyperglycaemia is associated with adverse lipid profiles in Europeans and Asians without a prior history of diabetes. There are distinct patterns of lipid profiles associated with ethnicity regardless of the glucose levels, suggesting that ethnic-specific strategies and guidelines on risk assessment and prevention of CVD are required. Dyslipidaemia predicts CVD in either diabetic or non-diabetic individuals defined based on the fasting glucose criteria, but not on the 2-hour criteria. The findings may imply considering different management strategies in people with fasting or post-load hyperglycaemia.

## TIIVISTELMÄ

Dyslipidemia, sydän-ja verisuonitautien (cardiovascular disease, CVD) merkittävä riskitekijä, on yleinen paitsi diabeetikoilla mutta myös henkilöillä, joilla on alentunut glukoosinsietokyky (impaired glucose tolerance, IGT) tai alentunut paastoverensokeri (impaired fasting glucose, IFG). Tutkimuksen tarkoituksena oli: 1) tutkia rasva-arvoja suhteessa glukoosiin eurooppalaisissa (I) ja aasialaisissa (II) väestöissä, joilla ei ole aiemmin todettu diabetesta, 2) tutkia eroja lipidiprofiileissa etnisten ryhmien välillä huomioiden plasman glukoosipitoisuus (III), 3) arvioida dyslepidemiaan liittyvän CVD-kuolleisuuden (IV) ja -sairastuvuuden (V) suhteellinen riski eri glukoosinsietokyvyn omaavilla henkilöillä.

Tutkimuksen aineisto koostuu 15 eurooppalaisesta kohortista, joihin osallistui yhteensä 19 476 tutkimushenkilöä (I ja III) ja 13 aasialaisesta kohortista, joihin osallistui 19 763 tutkimushenkilöä (II ja III). Näitä tutkimuksia, joissa tutkittiin 25-89-vuotiaita lähtökohtaisesti intialaisia, kiinalaisia, eurooppalaisia, japanilaisia ja Mauritiuksen intialaisia yhteensä 21 maasta, vertailtiin keskenään. Lipidi-CVD suhdetta tutkittiin 14 eurooppalaisessa kohortissa, joihin osallistui 17 763 miestä ja naista, joista selvisi myös kuolleisuusluvut. Keskimäärin 10 vuoden seurannan aikana (IV) havaittiin 871 CVD-peräistä kuolemaa. Kuudessa eurooppalaisessa tutkimuksessa arvioitiin dyslipidemian vaikutusta sepelvaltimotaudin ilmaantuvuuteen glukoositason mukaan (V). Lähtötilanteessa oli 9087 ilman sepelvaltimotautia olevaa henkilöä, joista 457:lle kehittyi sepelvaltimotauti seurannan aikana. Tutkimusten välisten menetelmäeroja vaikutuksen vähentämiseksi kunkin lipidi-komponentin analysoinnissa (I, II, IV ja V) käytettiin Z-score arvoja. Sepelvaltimotaudin kuolleisuus- ja sairastuvuusanalyysit suoritettiin käyttäen Coxin suhteellisen riskin regressioanalyysi huomioiden mahdolliset sekoittavat tekijät.

Kaikissa glukoosiluokissa paastoverensokerin (fasting plasma glucose, FPG) tasot korreloivat seerumin triglyseridipitoisuuden, kokonaiskolesterolin (total cholesterol, TC), TC-kolesterolin ja high-density lipoproteiini (HDL)-kolesterolin suhteen sekä ei-HDL-kolesterolin kanssa ( $p < 0.05$  useimmissa etnisissä ryhmissä) ja olivat käänteisesti yhteydessä HDL-kolesteroliin ( $p < 0.05$  joissakin, mutta ei kaikkissa populaatioissa). Lipidien ja 2-tunnin plasman glukoosipitoisuuden (2hPG) välinen yhteys oli samankaltainen kuin lipidien ja FPG:n yhteys, lukuunottamatta voimakkaampaa yhteyttä HDL-kolesterolin ja 2hPG välillä. Kun tutkittiin riskiä liittyen mataliin HDL-kolesteroliarvoihin käyttäen vertailuryhmänä eurooppalaisia henkilöitä, vakioidut riskisuhteet (odds ratio)(95% CI) olivat intialaisilla miehillä 4.74 (4.19-5.37), 5.05 (3.88-6.56), 3.07 (2.15-4.40) ja 2.37 (1.67-3.35) ja kiinalaisilla miehillä 0.12 (0.09-0.16), 0.07 (0.04-0.13), 0.11 (0.07-0.20) ja 0.16 (0.08-0.32), kun heillä oli joko normoglykemia, IGT tai IFG, diagnosoimaton diabetes tai

aikaisemmin diagnosoitu diabetes. Naisille saatiin samansuuntaiset tulokset. Matala HDL-kolesteroli oli yleisintä intialaisilla, mutta myös henkilöillä, joilla low-density lipoproteiini-kolesteroli oli yli 3mmol/l. Dyslipidemia oli yhteydessä lisääntyneeseen CVD-kuolleisuuteen tai sepelvaltimotaudin ilmaantuvuuteen henkilöillä, joilla oli yksinomainen paastohyperglykemia tai IFG, mutta ei niillä, joille oli yksinomainen glukoosirasituksen jälkeinen hyperglykemia tai IGT.

Yhteenvetona voidaan todeta, että hyperglykemia on yhteydessä haitallisiin lipidiprofiileihin eurooppalaisilla ja aasialaisilla, joilla ei ole aikaisemmin todettua diabetesta. Määrätynlaiset lipidiprofiilit ovat yhteydessä etniseen alkuperään veren glukoositasoista riippumatta, mikä viittaa siihen, että eri etnisissä ryhmissä tarvitaan omat strategiat ja suuntaviivat CVD:n riskinarvioinnissa ja ehkäisyssä. Dyslipidemia ennustaa CVD:tä, riippumatta siitä, onko henkilöllä todettavissa diabetes paastoveren glukoosikriteerin perusteella, mutta se ei ennusta henkilöllä, joilla on todettavissa diabetes 2 tunnin glukoosirasituksen jälkeisen kriteerin mukaan. Tulosten perusteella voidaan mahdollisesti harkita eri hoitosuosittelujen käyttöä ihmisillä, joilla on paastoveren glukoosi koholla kuin niillä, joilla on hyperglykemia glukoosirasituksen jälkeen.

# 1 INTRODUCTION

Cardiovascular disease (CVD) is a major cause of death worldwide (World Health Organization 2007). Although mortality from CVD has decreased in many European and other western countries over the past decades, the epidemic of CVD is being an increasing public health challenge in Asia with growing urbanization and industrialization (Zimmet et al. 2001; Ramachandran et al. 2008). Dyslipidaemia is one of the major CVD risk factors and plays an important role in the progress of atherosclerosis, the underlying pathology of CVD. To control abnormal lipids and lipoproteins levels has been recommended by different national, regional, or global (Expert Panel 2001; Graham et al. 2007; World Health Organization 2007) guidelines on the prevention and management of CVD.

Dyslipidaemia often coexists with diabetes, the coronary heart disease (CHD) risk equivalent. An atherogenic lipid profile, consisting of high triglycerides (TG) and small dense low-density lipoprotein cholesterol (LDL-C) and low high-density lipoprotein cholesterol (HDL-C), is common not only in patients with overt diabetes (Barrett-Connor et al. 1982) but also in individuals with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) (Meigs et al. 2002; Novoa et al. 2005; Chen et al. 2006; Pankow et al. 2007). Nevertheless, none of the cross-sectional studies has evaluated the linear relationship between lipid and blood glucose concentrations at levels below the current diagnostic thresholds for diabetes in either the Europeans or the major ethnic groups of Asian populations.

The importance of dyslipidaemia on risk of CVD in patients with diabetes has been extensively studied in numerous studies. Reduced HDL-C is well documented as an independent predictor of CVD events (Wilson et al. 1988; Cooney et al. 2009). In contrast, the role of TG as an independent risk factor for CVD is more controversial (Patel et al. 2004; Psaty et al. 2004; Barzi et al. 2005; Sarwar et al. 2007; Wang et al. 2007). Recently, the interest to use novel parameters such as total cholesterol (TC) to HDL ratio (TC/HDL-C), non-HDL-cholesterol (non-HDL-C), apolipoprotein B (apoB) and apolipoprotein A (apoA) to assess CVD risk has increased (Barzi et al. 2005; Pischon et al. 2005; Charlton-Menys et al. 2009). As a CVD risk predictor, the non-HDL-C has been considered to be superior to LDL-C (Cui et al. 2001; Schulze et al. 2004; Liu et al. 2005; Ridker et al. 2005). But little is known with regard to the impact of these dyslipidaemic parameters on cardiovascular mortality or morbidity in individuals with non-diabetic glucose levels.

## 2 REVIEW OF THE LITERATURE

### 2.1 Physiology of lipid metabolism

Lipids are fats that are either absorbed from blood or synthesized by the liver. All lipids are hydrophobic and therefore they are transported associated with proteins as lipoproteins (Table 1), which are hydrophilic and with spherical structures.

Table 1 Physical properties, lipid and apolipoprotein composition of human plasma lipoproteins

	Chylomicron	VLDL	IDL	LDL	HDL
Source	Intestine	Liver	Lipolysis of VLDL	Lipolysis of VLDL, via IDL	Liver, intestine;
Diameter (nm)	75-1200	30-80	25-35	18-25	5-12
Density (kg/l)	< 0.96	0.96-1.006	1.006-1.019	1.019-1.063	1.063-1.210
Composition (%)					
Triglycerides	86	55	23	6	5
Phospholipids	7	18	19	22	33
Cholesteryl esters	4	12	29	42	17
Free cholesterol	2	7	9	8	5
Protein	2	8	19	22	40-55
Apolipoproteins contained	A-I, A-IV, B-48, C, E	B-100, C, E	B-100, C, E	B-100	A-I, A-II, C, E

VLDL, very-low density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

#### 2.1.1 Exogenous lipid metabolism

Over 95% of dietary lipids are TG; the rest are phospholipids, free fatty acids (FFA), cholesterol and fat-soluble vitamins. Dietary fats are digested in the stomach and duodenum into monoglycerides (MGs) and FFAs by gastric lipase, pancreatic lipase and emulsification from vigorous stomach peristalsis (Fig. 1). Dietary cholesterol esters are de-esterified into free cholesterol (FC) by the same mechanisms. MGs, FFAs and FC are then solubilized in the intestine by bile acid micelles, which shuttle them to intestinal villi for absorption. They are reassembled into TGs and packaged with cholesterol into chylomicrons once absorbed into the enterocytes.

Chylomicrons, the largest lipoproteins, transport dietary TG and cholesterol from within enterocytes through lymphatics into the circulation. In the capillaries of adipose and muscle

tissues, apolipoprotein C-II (apoC-II) on the chylomicron activates endothelial lipoprotein lipase (LPL) (Breckenridge et al. 1978) to convert 90% of chylomicron TG to fatty acids and glycerol, which are taken up by adipocytes and muscle cells for energy use or storage (Fig. 1). Cholesterol-rich chylomicron remnants are then cleared rapidly from circulation by the liver through a process mediated by apolipoprotein E (apoE) (Mahley and Ji 1999).

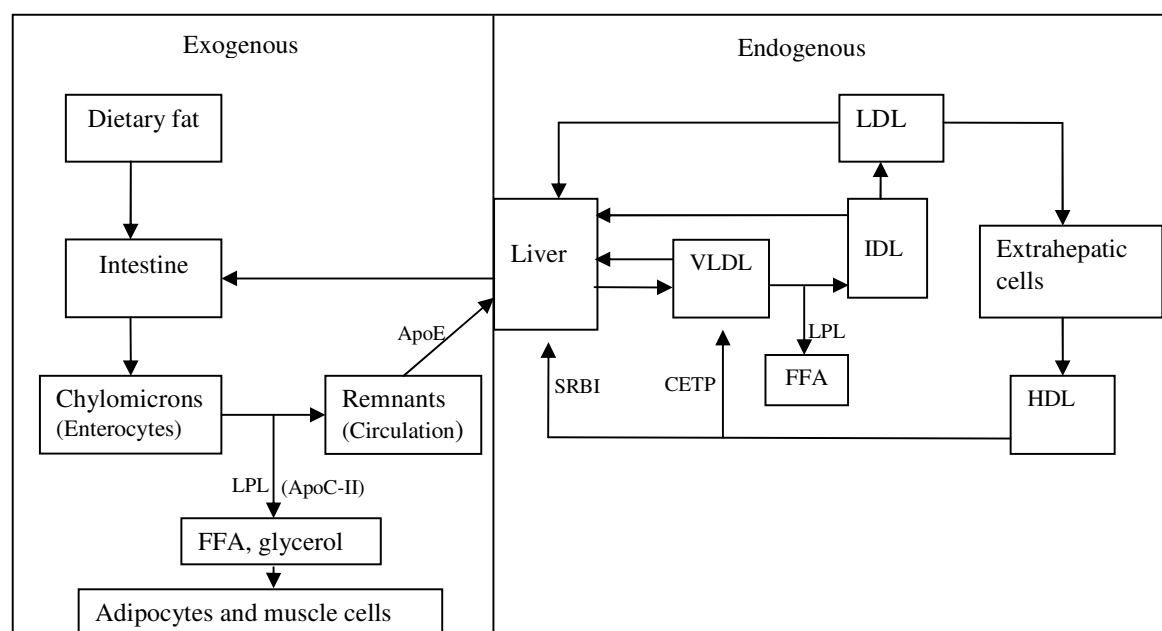


Figure 1 Summary of exogenous and endogenous lipid metabolism. FFA: free fatty acid; LDL: low-density lipoprotein; IDL: intermediate-density lipoprotein; HDL: high-density lipoprotein; LCAT: lecithin-cholesterol acyl transferase; LPL: lipoprotein lipase; ApoC-II: apolipoprotein C-II; SRBI: scavenger receptor class B type I; CETP: cholesteryl ester transfer protein

## 2.1.2 Endogenous lipid metabolism

Lipoproteins synthesized by the liver transport endogenous TGs and cholesterol (Fig. 1). Lipoproteins circulate through the blood continuously until the TGs are taken up by peripheral tissues or the lipoproteins themselves are cleared by the liver. They become more cholesterol-rich by the loss of TGs. Therefore factors that stimulate hepatic lipoprotein synthesis generally lead to elevated plasma cholesterol.

Very-low-density lipoproteins (VLDL) containing apoB-100, are synthesized in the liver, and transport TG and cholesterol to peripheral tissues. VLDL is the way the liver exports excess intrahepatic FFA, such as occurs with high-fat diets and when excess adipose tissue releases FFAs directly into the circulation (eg, in obesity, uncontrolled diabetes). ApoC-II

on the VLDL surface activates endothelial LPL to hydrolyze TGs into FFAs and glycerol, which are taken up by cells.

Intermediate-density lipoproteins (IDL) are the product of LPL processing of VLDL and chylomicrons (Eisenberg 1984). IDL are cholesterol-rich VLDL and chylomicron remnants that are either cleared by the liver or metabolized by hepatic lipase into LDL, which retains apoB (Poapst et al. 1985; Steiner et al. 1987).

LDL, the products of VLDL and IDL catabolism, are the most cholesterol-rich of all lipoproteins. About 40-60% of all LDL are cleared by the liver in a process mediated by apoB and hepatic LDL receptors (Attie et al. 1982); the rest are taken up by either non-hepatic LDL or non-hepatic scavenger receptors. Hepatic LDL receptors are down-regulated by delivery of cholesterol to the liver and by increased dietary saturated fat (Spady and Dietschy 1985; Fox et al. 1987). Non-hepatic scavenger receptors, most notably on macrophages, take up excess oxidized LDL not processed by hepatic receptors. Monocytes rich in oxidized LDL migrate into the subendothelial space and become macrophages, which takes up more oxidized LDL and form foam cells within atherosclerotic plaques. There are 2 forms of LDL: large, buoyant and small, dense LDL (Austin et al. 1988b; Barakat et al. 1990). Small, dense LDL is especially rich in cholesterol esters, associated with metabolic disturbances such as hypertriglyceridaemia, insulin resistance and atherogenesis (Austin et al. 1988a; Aguilera et al. 2008). The increased atherogenicity of small, dense LDL derives from less efficient hepatic LDL receptor binding, leading to prolonged circulation and exposure to endothelium and increased oxidation (Nigon et al. 1991).

The overall role of HDL, synthesized in both enterocytes and the liver, is to obtain cholesterol from peripheral tissues and other lipoproteins and transport it to other cells, other lipoproteins (using cholesteryl ester transfer protein [CETP]) and the liver. Efflux of FC from cells (Johnson et al. 1986) is mediated by adenosine triphosphate-binding cassette transporter A1 (ABCA1), which combines with apoA-I to produce nascent HDL. FC in nascent HDL is then esterified by the lecithin-cholesterol acyl transferase (LCAT), producing mature HDL (Rye et al. 1999; Santamarina-Fojo et al. 2000). HDL exerts various anti-atherogenic properties, including reverse transport of cholesterol from cells of the arterial wall to the liver (Miller et al. 1985; Tall 1998), inhibition of LDL oxidation by HDL-bound paraoxonase-1 (Mackness et al. 1993; Mackness et al. 1996), regulation of coagulation and fibrinolysis and inhibition of platelet activation (Nofer et al. 2002), neutralization of endotoxin or lipopolysaccharide (Huuskonen et al. 2001), inhibition of the



chemotaxis of monocytes and the adhesion of leukocytes to the endothelium (Nofer et al. 2002) and promotion of endothelial progenitor cell-mediated endothelial repair (Sumi et al. 2007).

Lipoprotein(a) [Lp(a)] is LDL that contains apolipoprotein(a), characterized by 5 cysteine-rich regions called kringle. One of these regions is homologous with plasminogen and is thought to competitively inhibit fibrinolysis and thus predispose to thrombus (Jialal 1998; Maher and Brown 1995). Because Lp(a) has LDL as its component, oxidized Lp(a) is avidly taken up by the scavenger receptor pathway and promotes cholesterol delivery into the artery wall (Jialal 1998), inducing atherosclerosis.

## **2.2 Epidemiology of dyslipidaemia**

### **2.2.1 Prevalence and ethnic variation**

Lipids and lipoproteins abnormalities are major metabolic disorders, commonly including elevated levels of TC, LDL-C, Lp(a) and TG and reduced levels of HDL-C. In patients with type 2 diabetes, a CHD equivalent (Juutilainen et al. 2005), it is most commonly characterized by elevated TG and reduced HDL-C (Goldberg 2001; Krauss 2004; Kendall 2005). These abnormalities can be present alone or in combination with other metabolic disorders. The prevalence of dyslipidaemia varies depending on the population studied, geographic location, socioeconomic development and the definition used (Wood et al. 1972; Onat et al. 1992; Berrios et al. 1997; Ezenwaka et al. 2000; Foucan et al. 2000; Hanh et al. 2001; Zaman et al. 2001; Li et al. 2005; Pang et al. 2006; Zhao et al. 2007; Erem et al. 2008; Azizi et al. 2003; Pongchaiyakul et al. 2006; Mann et al. 1988; Hertz et al. 2006; Tekes-Manova et al. 2006; Steinhagen-Thiessen et al. 2008; Florez et al. 2005). Caucasians generally have higher mean TC concentrations than do populations of Asian or African origin (Fuentes et al. 2003; Tolonen et al. 2005). In general populations, the highest prevalence of hypercholesterolaemia (TC  $\geq$  6.5mmol/l) has been seen in Malta (up to 50% in women) and the lowest in China (2.7% in men) in the World Health Organization (WHO) Inter-Health Programme (Berrios et al. 1997). However, inhabitants of the developing world now have had access to more fats in their diets and more sedentary lives; therefore the disease is becoming an increasing problem there.

There is a large body of evidence showing that diabetes is associated with a high prevalence of dyslipidaemia (Kannel 1985; Cowie et al. 1994; UKPDS Investigators 1997; Jacobs et al. 2005; Bruckert et al. 2007; Okafor et al. 2008; Surana et al. 2008; Ahmed et al. 2008;

Abdel-Aal et al. 2008; Jurado et al. 2009; Papazafiropoulou et al. 2009; Roberto Robles et al. 2009; Seyum et al. 2010; Agarwal et al. 2009; Temelkova-Kurktschiev et al. 2009; Zhang et al. 2009). In the Framingham Heart Study (Kannel 1985), the prevalence of low HDL-C (21% vs. 12% in men and 25% vs. 10% in women, respectively) and high TG levels (19% vs. 9% in men and 17% vs. 8% in women, respectively) in people with diabetes was almost twice as high as the prevalence in non-diabetic individuals. By contrast, TC and LDL-C levels did not differ from those of non-diabetic counterparts. A similar pattern of lipid profiles was observed in the UK Prospective Diabetes Study (UKPDS) (UKPDS Investigators 1997). In this study, the plasma TG levels were substantially increased whereas HDL-C levels were markedly reduced in both men and women with diabetes compared with the non-diabetic controls. Higher prevalence has been reported in other studies. Data from a primary care-based 7692 patients with type 2 diabetes in the United States showed nearly half of the patients had low HDL-C (Grant and Meigs 2007). The figure was even worse in an urban Indian cohort of 5088 type 2 diabetes patients, with more than half having low HDL-C (52.3%) or high TG (57.9%) (Surana et al. 2008). In addition to the traditional lipid measurement, increased levels of apoB were also seen in patients with diabetes compared with non-diabetic individuals (Bangou-Bredent et al. 1999).

It has been shown that the prevalence of lipid and/or glucose abnormality differs between ethnic groups. It is clear that certain ethnic groups have differences in lipid profiles in general. Elevated TG and reduced HDL-C, as the components of the metabolic syndrome and atherogenic dyslipidaemia, was seen more common in Asian Indians than in the whites (Anand et al. 2000; Razak et al. 2005; Chandalia et al. 2008; Mulukutla et al. 2008), Chinese (Tan et al. 1999; Anand et al. 2000; Razak et al. 2005; Karthikeyan et al. 2009; The DECODA Study Group 2007), Japanese (Karthikeyan et al. 2009; The DECODA Study Group 2007) or Africans (Mulukutla et al. 2008). In a nationally representative sample of seven ethnic groups in the UK (Zaninotto et al. 2007), the prevalence of low HDL-C was highest in south Asian groups such as Bangladeshi, Indian and Pakistani, followed by Chinese, Irish and those from the general population living in private households; In contrast, the lowest prevalence was seen in black Caribbean. Similar finding was reported in another study where the comparison was made between non-South-Asians and South Asians (France et al. 2003). In addition, African Americans have been reported to have less adverse lipid profiles than Whites or Hispanics despite the presence of diabetes (Sharma and Pavlik 2001; Cowie et al. 1994; Werk et al. 1993). The causes of ethnic difference in levels of CVD risk factor are complex and may include genetic, environmental and cultural factors (Zaninotto et al. 2007). However, little is known about such ethnic differences in lipid profiles at comparable glucose tolerance status.

### **2.2.2 Risk factors**

There are several factors that contribute to the development of dyslipidaemia (Expert Panel 2001), including genetic factors (Cohen et al. 1994) and acquired factors (Chait and Brunzell 1990; Devroey et al. 2004; Ruixing et al. 2008) such as overweight and obesity (Denke et al. 1993; Denke et al. 1994; Brown et al. 2000), physical inactivity (Berg et al. 1997; Hardman 1999), cigarette smoking (Criqui et al. 1980; Cade and Margetts 1989; Umeda et al. 1998; Fisher et al. 2000; Wu et al. 2001; Maeda et al. 2003; Mammass et al. 2003; Venkatesan et al. 2006; Grant and Meigs 2007; Batic-Mujanovic et al. 2008; Arslan et al. 2008), high fat intake (Millen et al. 2002; Hennig et al. 2001; Tanasescu et al. 2004), very high carbohydrate diets (> 60 percent of total energy) (McNamara and Howell 1992) and certain drugs (Lehtonen 1985; Fogari et al. 1988; Roberts 1989; Middeke et al. 1990; Stone 1994) (such as beta-blockers, anabolic steroids, progestational agents, et al.). Excess alcohol intake is also documented as a risk factor (Umeda et al. 1998; Wu et al. 2001; Mammass et al. 2003) despite that moderate alcohol consumption may have a beneficial effect on improving HDL-C concentrations (De Oliveira et al. 2000; Shai et al. 2004b). In addition, glycaemic control is an important determinant of dyslipidaemia in patients with diabetes (Ismail et al. 2001; Grant and Meigs 2007; Ahmed et al. 2008; Gatti et al. 2009). Among these acquired factors, overweight, obesity and physical inactivity appear to be most important (Denke et al. 1993; Denke et al. 1994; Hardman 1999; Berg et al. 1997; Brown et al. 2000). They are also the most important lifestyle variables that decrease insulin action and increase the risk of diabetes.

## **2.3 Dyslipidaemia in individuals with hyperglycaemia: the role in the progress of atherosclerosis**

The origins of the diabetic dyslipidaemia derive from specific abnormalities in lipoprotein metabolism and abnormalities in insulin action. The most fundamental defect in these patients is resistance to cellular actions of insulin, particularly resistance to insulin-stimulated glucose uptake (Ginsberg 2000; Avramoglu et al. 2006). In both fasting and postprandial states, deficient action of insulin on adipocytes results in reduced suppression of lipolysis of stored TG, increasing the release of FFA. Higher uptake of FFAs in the liver results in an increased hepatic production of VLDL (Howard 1987; Lewis 1997). The reduced action of insulin also impairs LPL action, resulting in impaired clearance of VLDL from the circulation. The final result is an elevation of circulating TG concentration.

A low level of HDL-C is closely linked to the overproduction of TG-rich lipoproteins such as VLDL and chylomicrons (Bakogianni et al. 2001; Semenkovich 2006). In the hypertriglyceridaemic, insulin resistant states, it is enhanced that TG-rich lipoproteins actively exchange their core lipid with both HDL and LDL, a process facilitated by CETP (Hayek et al. 1993). This results in TG enrichment of HDL and LDL. Although the mechanisms are not entirely clear, available data suggest TG-enrichment of HDL particles leading to particle instability and degradation, enhancing catabolism of HDL (Rashid et al. 2003). ApoA-I may dissociate from TG-enriched HDL and is then cleared rapidly from plasma, further reducing the availability of HDL for reverse cholesterol transport. It is also possible that insulin resistance and low HDL-C levels may have a common mediator such as tumor necrosis factor- $\alpha$  that is found to down-regulate the apoA-I gene expression and can lower serum HDL-C levels (Haas et al. 2003). On the other hand, TG-enriched LDL particles due to the hypertriglyceridaemia and increased CETP activity undergo lipolysis and thus convert into small dense LDL (Kendall 2005).

Diabetic dyslipidaemia is a major predisposing factor to the development of atherosclerosis (Syvanne and Taskinen 1997). Small dense LDL particles penetrate the endothelial barrier 1.7 times more easily than do larger LDL particles, and they remain longer in the subendothelial matrix (de Graaf et al. 1991). Moreover, small dense LDL particles are more easily modified by oxidation and, particularly in type 2 diabetes, by glycation, and are more atherogenic (Brinton 2005). Oxidative modification of LDL particles results in rapid uptake by macrophages, with subsequent formation of foam cells (Pastromas et al. 2008). LDL particles can promote inflammatory and immune changes via cytokine released from macrophages (Hammad et al. 2009). Foam cells can rupture and release oxidized LDL particles, intracellular enzymes and oxygen-free radicals that can further damage the vessel wall. The increased synthesis of VLDL particles are taken up by receptors located on macrophages, thus promoting the accumulation of lipids within macrophages and contributing to the formation of foam cells in vessel walls as well. Furthermore, hypertriglyceridaemia is associated with prothrombotic and inflammatory changes that may contribute to the increased risk of CVD (Krentz 2003). HDL from patients with type 2 diabetes may have substantially impaired endothelial-protective effects compared with HDL from healthy subjects (Sorrentino et al. 2010). In addition, low HDL may disturb reverse cholesterol transport, a process by which excess amounts of cholesterol located in cells and atherosclerotic plaques are removed (Gotto and Brinton 2004).

## **2.4 Relationship between dyslipidaemia and cardiovascular risk in individuals with different glucose levels**

In the past decades, genetic, histopathologic and epidemiological studies have established the primary role of lipids and lipoproteins in the development of CVD, either in general population or in patients with diabetes. It is well-established that TC, LDL-C, low HDL-C and calculated indices such as TC/HDL-C or non-HDL-C are predictors of cardiovascular events. Whether fasting TG is an independent predictor of CVD, however, remains unsettled.

### **2.4.1 Lipids and cardiovascular risk in general populations**

The link between levels of TC and the risk of CHD has been well established. There is a strong and graded positive association between TC as well as LDL-C and the risk of CHD (Neaton et al. 1992; Nobili et al. 1994). Data from the the Multiple Risk Factor Intervention Trial (MRFIT) study (LaRosa et al. 1990) demonstrate a curvilinear relation between TC level and CHD mortality. Clinical trials using lipid-modifying drugs have unequivocally demonstrated that lowering LDL-C yields significant reductions in both morbidity and mortality from CHD in people with or without established CHD (Mills et al. 2008; Thavendiranathan et al. 2006), supporting that the reduction of LDL-C should be of prime concern in both primary and secondary prevention of atherosclerotic disease.

The role of HDL-C as an independent and powerful inverse predictor of CHD has been well established (Gordon et al. 1977; Rywik et al. 1999; Cui et al. 2001; Mazza et al. 2005; Bass et al. 1993; The DECODE Study Group 2006; Barzi et al. 2005; Tanko et al. 2005; Tunstall-Pedoe et al. 1997; Laakso et al. 1993; Ridker et al. 2005; Pischon et al. 2005; Zaninotto et al. 2007; Cooney et al. 2009). An analysis of data from the Framingham study, the Coronary Primary Prevention Trial (CPPT), and the MRFIT study indicates that the risk for CHD decreases by 2%-3% for each 0.03 mmol/l increase in HDL-C, after controlling for other risk factors (Gordon et al. 1989). In the Lipid Research Clinics Prevalence Mortality Follow-up Study (LRCF), the same increment (0.03 mmol/l) in HDL-C was associated with a significant CVD mortality decrement of 3.7% in men and 4.7% in women (Gordon et al. 1989). Although the benefits of raising HDL-C levels remain to be confirmed in randomized clinical trials, it appears in a most recent report that the modest improvement in HDL-C levels (per 0.13 mmol/l) is associated with a 21% reduction in cardiovascular risk independent of the effect on other lipid measures (Grover et al. 2009).

The association between hypertriglyceridaemia and risk of CVD is not as strong as it is for TC and HDL-C. High TG is consistently shown to be a significant CVD risk factor in most of the univariate analyses (Stampfer et al. 1996; Cremer et al. 1997; Dunder et al. 2004a; Eberly et al. 2003; Hulley et al. 1980; Iso et al. 2001; Jeppesen et al. 2001; Pirro et al. 2002; Pischon et al. 2005; Psaty et al. 2004; Shai et al. 2004a; Sharrett et al. 2001; Talmud et al. 2002; Yarnell et al. 2001; Bansal et al. 2007) and in some of the multivariate models including HDL-C (Eberly et al. 2003; Iso et al. 2001; Jeppesen et al. 2001; Sharrett et al. 2001; Stampfer et al. 1996; Talmud et al. 2002; Yarnell et al. 2001; Bansal et al. 2007) but not in others (Avins and Neuhaus 2000; Cremer et al. 1997; Dunder et al. 2004a; Eberly et al. 2003; Hulley et al. 1980; Pirro et al. 2002; Pischon et al. 2005; Shai et al. 2004a; Sharrett et al. 2001; Talmud et al. 2002; Walldius et al. 2001; Yarnell et al. 2001; Bansal et al. 2007). In many early prospective studies, the predictive value of fasting TG tended to diminish or even disappear when other lipid or non-lipid risk factors were considered. This failure may result from the large number of intercorrelated variables associated with elevated TG. Renewed interest in the importance of elevated TG has been, however, stimulated by the publication of meta-analyses that found that raised TG is in fact an independent risk factor for CHD (Austin et al. 1998; Assmann et al. 1998). A number of epidemiological studies published in the past few years (Dunder et al. 2004a; Eberly et al. 2003; Pischon et al. 2005; Shai et al. 2004a) have also supported the role of TG as an independent risk factor. Thus, many persons with elevated TG are at increased risk for CHD, even when this greater risk cannot be independently explained by TG.

Recently, the use of TC/HDL-C (Barzi et al. 2005; Ridker et al. 2005) and non-HDL-C (Cui et al. 2001) for CVD risk assessment has increased. The Framingham Heart Study and the Quebec Cardiovascular Study have demonstrated that TC/HDL-C appears to predict CHD events better than any single lipid parameter (Natarajan et al. 2003; Lemieux et al. 2001). Non-HDL-C is also shown to be a better predictor of CVD mortality than LDL-C (Cui et al. 2001; Schulze et al. 2004; Liu et al. 2005; Ridker et al. 2005) because it includes all atherogenic lipoprotein particles.

In addition, ApoB and apoB/apoA-I are useful indicators of risk of atherosclerosis. Data from the Health Professionals Follow-up Study, a nested case-control study with a 6-year follow up of 18,225 male participants, showed that apoB is more predictive in development of CHD than non-HDL-C (Pischon et al. 2005). The finding from the INTERHEART study, another case-control study with 21,465 participants from 262 centres in 52 countries, strengthened the predictive ability of apoB/apoA1 for myocardial infarction (MI)

(McQueen et al. 2008). This has been supported by recent reports from prospective studies, such as Apolipoprotein Mortality Risk study (Walldius et al. 2001), the European Prospective Investigation of Cancer-Norfolk study (Vaessen et al. 2006), Uppsala Longitudinal Study of Adult Men (Dunder et al. 2004b) and the MONItoring of trends and determinants in Cardiovascular disease Augsburg/KOoperative Gesundheitsforschung in der Region Augsburg (Meisinger et al. 2005). In a most recent report from the Third National Health and Nutrition Examination Survey mortality study, the predictive ability of apoB to detect CHD death was better than any of the routine clinical lipid measurement and as powerful as apoB/apoA-I (Sierra-Johnson et al. 2009). Whereas, standardized apoB measures are not widely available and apoB is not included in the current recommendations for assessing cardiovascular risk.

#### **2.4.2 Lipids and cardiovascular risk in individuals with hyperglycaemia**

It is well known that the risk of morbidity and mortality from CVD is increased by two- to four-fold in diabetic patients compared with the general population (Kannel 1985; Morrish et al. 1991b; Almdal et al. 2004). A number of studies have determined the association of dyslipidaemia with cardiovascular risk in people with hyperglycaemia, and most of them were conducted in patients with diabetes. There is a large body of evidence linking dyslipidaemia and cardiovascular risk in patients with diabetes against quite few negative reports (Roselli della Rovere et al. 2003; Vlainjac et al. 1992) on this issue. Cross-sectional studies have found positive associations of atherosclerotic vascular disease with TC (Ronnemaa et al. 1989; Jurado et al. 2009), LDL-C (Reckless et al. 1978; Jurado et al. 2009; Agarwal et al. 2009), non-HDL-C (Jurado et al. 2009), TG (Santen et al. 1972; Ronnemaa et al. 1989; Gomes et al. 2009), apoB (Ronnemaa et al. 1989) and Lp(a) (Mohan et al. 1998; Murakami et al. 1998; Smaoui et al. 2004), but inverse associations with HDL-C (Reckless et al. 1978; Ronnemaa et al. 1989; Smaoui et al. 2004; Grant and Meigs 2007; Jurado et al. 2009; Gomes et al. 2009) and apoA-I (Seviour et al. 1988; Ronnemaa et al. 1989).

Prospective data have provided with further evidence. The UKPDS study (Turner et al. 1998) has demonstrated that high LDL-C and low HDL-C are potentially modifiable risk factors for coronary artery disease (CAD) in patients with type 2 diabetes. TG, however, was not independently associated with CAD risk in this study, possibly because of its close inverse relationship with HDL-C. Results from the MRFIT (Stamler et al. 1993), in which 356,499 nondiabetic and 5163 diabetic men without CHD at baseline were followed for 12 years, indicated that serum cholesterol is an independent predictor of CHD mortality in men with diabetes. Rosengren et al. (Rosengren et al. 1989) showed similar results in a

prospective study of 6897 middle aged diabetic men. Patients with TC > 7.3 mmol/l had a significantly higher incidence of CHD during the 7-year follow up than those with TC ≤ 5.5 mmol/l (28.3% vs. 5.4%, p<0.05). Long term follow-up of the London cohort of the WHO Multinational Study of Vascular Disease in Diabetics, consisting of 254 type 2 diabetic patients, has showed that TC was associated with incidence of MI (Morrish et al. 1991a) and overall cardiovascular mortality (Morrish et al. 1990). The role of TC in predicting CHD was also confirmed in women patients with diabetes (Schulze et al. 2004).

In general, the lipid profile in patients with type 2 diabetes is most commonly characterized by hypertriglyceridaemia and reduced HDL-C. Most of the studies consistently addressed the role of HDL-C in predicting CVD in patients with hyperglycaemia. In the Honolulu Heart Program (Laws et al. 1993), both HDL-C and TC were significant predictors of incident CHD in men with diabetes (diagnosis based on use of oral hypoglycaemic agent) or abnormal glucose tolerance (1-h glucose ≥ 12.5 mmol/l after 50 g oral glucose challenge), independently of age, body mass index (BMI), systolic blood pressure (SBP), smoking and alcohol consumption. In the Helsinki Heart Study, both low HDL-C and high LDL-C were independently related to CHD incidence in 135 diabetic patients during a 5-year follow-up (Koskinen et al. 1992). Laakso et al. (Laakso et al. 1993) gave further evidence in a Finnish cohort that low HDL-C and HDL<sub>2</sub> cholesterol are powerful risk indicators for CHD events in 313 diabetic patients during a 7-year follow-up.

Although the role of TG in predicting cardiovascular events remains controversial in the general population, the evidence in diabetic populations is better established (Janka 1985; Koskinen et al. 1992; Laakso et al. 1993; Uusitupa et al. 1993; Turner et al. 1998; Bos et al. 2003; Chan et al. 2005; Tseng et al. 2006; Fontbonne et al. 1989; West et al. 1983; Giorda et al. 2008). In the WHO multinational study, ischaemic heart disease was more strongly associated with TG than with TC concentrations, particularly in obese diabetic patients (West et al. 1983). During an 11-year follow-up of 943 patients with either IGT or diabetes in the Paris Prospective Study, TG was the only factor significantly associated with coronary deaths in multivariate regression analysis (Fontbonne et al. 1989). In the Schwabing Study of 542 diabetic patients, TG was shown to be a significant predictor of 5-year incidence of major macrovascular complications such as cardiovascular death, gangrene or MI (Janka 1985). Data from a Finnish study (Laakso et al. 1993) showed that both high total and VLDL-TG were predictive for CHD events in 313 diabetic patients who were followed up for 7 years. In another Finnish study, LDL-TG but not total TG was found to be associated with cardiovascular death (Uusitupa et al. 1993). This may be due to the



impact of LDL particles enriched with TG on atherogenesis. The role of TG was also confirmed separately in women patients with type 2 diabetes enrolled in the Nurses' Health Study (Schulze et al. 2004). In addition, data from diabetic populations other than Caucasian patients confirmed the predictive value of TG. Chan and colleagues (Chan et al. 2005), following 517 Chinese patients with newly diagnosed type 2 diabetes for 4.6 years, found that TG was significantly associated with cardiovascular mortality in these patients. These epidemiological findings have been supported by randomized clinical trials in which reduction of TG was related to decreased risk of CVD in patients with low HDL-C (Rubins et al. 1999; Keech et al. 2005).

In the Hoorn Study (Bos et al. 2003), high TG was shown to be a risk factor for CVD in subjects with diabetes or prediabetes, but only in those with high non-HDL-C. This finding, together with other raising evidence, implies that non-HDL-C may be a useful marker for CVD not only in the general population (Cui et al. 2001; Liu et al. 2005; Pischon et al. 2005; Rallidis et al. 2005) but also in diabetic patients (Lu et al. 2003; Jiang et al. 2004; Schulze et al. 2004). In the Strong Heart study, a 9-year follow-up study of 2108 American-Indian patients with diabetes but free of CVD at baseline, non-HDL-C (highest vs. lowest tertile) was strongly associated with incidence of overall CVD in both male [HR 2.23 (1.41–3.43)] and female [1.80 (1.32–2.46)] patients (Lu et al. 2003). The finding was further confirmed in diabetic men in the Health Professionals' Follow-up Study (Jiang et al. 2004). However, among diabetic women in the Nurses' Health Study (Schulze et al. 2004), non-HDL-C predicted CHD risk only among those with elevated TG levels, implying that non-HDL-C may provide little additional power to predict CHD at lower TG levels.

Recently, the utility of TC/HDL-C as CVD predictor is increasing in diabetic population and has been evaluated in several studies. TC/HDL-C is as good as non-HDL-C in the Strong Heart Study (Lu et al. 2003) and is shown to be the best predictor in diabetic men in the Health Professionals' Follow-up Study (Jiang et al. 2004), but failed to be predictive in diabetic women in the Nurses' Health Study (Schulze et al. 2004).

Previous studies have shown that patients with diabetes have elevated apoB (Bangou-Bredent et al. 1999; Thomas et al. 2006), apoC-III/C-II, apoE and decreased concentrations of apoA-I (Thomas et al. 2006). In two prospective studies, apoB seems to be a potent predictor of CVD in both diabetic men (Jiang et al. 2004) and women (Schulze et al. 2004). Nevertheless, a large body of evidence is still limited concerning the role of apoB in predicting CVD risk in diabetic patients.

Although the role of lipid parameters in predicting cardiovascular risk has, as above summarized, been well addressed in either general or diabetic populations, it is still unclear that whether lipids predict CVD/CHD events in people with prediabetes (i.e., IGT and IFG), who are already exposed to a cluster of risk factors.

## **2.5 Management of dyslipidaemia**

Epidemiological investigations of human populations have revealed a robust relationship between lipids and CVD risk. Furthermore, the benefit of lipid-modifying strategy on cardiovascular events has been demonstrated from a large number of randomized clinical trials (Mills et al. 2008; Thavendiranathan et al. 2006), especially from those using 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors (i.e., statins) (Colhoun et al. 2004; Pyorala et al. 2004; Collins et al. 2003; Goldberg et al. 1998; Shepherd et al. 2006; Sever et al. 2005; Knopp et al. 2006). Intensive control of dyslipidaemia has been greatly emphasized in the prevention and management of CVD. Current guidelines from the National Cholesterol Education Program Adult Treatment Panel III (ATP III) (Adult Treatment panel III 2002), the European Society of Cardiology (Graham et al. 2007) and the American Diabetes Association (American Diabetes Association 2009) consistently recommend that LDL-C should be the primary target of therapy not only in patients with CHD or diabetes but also in persons with increased cardiovascular risk. In addition, non-HDL-C is set by ATP III as a secondary target of therapy and HDL-C and TG as potential target.

Despite current guidelines aimed at achieving targets for LDL-C, blood pressure and glycaemia, patients remain at high residual risk of vascular events (Fruchart J 2008). Dyslipidaemia may play a role in residual vascular risk. LDL-C, however, is not the sole lipid that defines the risk. Therapies which aim to raise HDL-C are currently under intense consideration. Recent evidence (Grover et al. 2009) supports the further evaluation of therapies to raise HDL-C levels to prevent cardiovascular events. In a most recent study, extended-release niacin (ERN) therapy is shown to not only increase plasma HDL-C levels but also substantially improve endothelial-protective properties of HDL in diabetic patients (Sorrentino et al. 2010). Moreover, ERN therapy in combination with a statin induces regression of carotid intima-media thickness in patients with CHD or CHD equivalent (Villines et al. 2010). The current evidence implies that pharmacological HDL-raising therapies should be examined in the way their ability to restore the vascular-protective function of HDL.

### **3 AIMS OF THE STUDY**

The aims of this study are:

- 1) To investigate lipid profiles in relation to plasma glucose levels in European men and women without a prior history of diabetes (Study I);
- 2) To study blood lipid levels in relation to plasma glucose levels in 7 Asian populations without a prior history of diabetes (Study II);
- 3) To compare the ethnic difference in lipid profiles controlling for plasma glucose levels in European and Asian populations (Study III);
- 4) To assess the impact of dyslipidaemia on CVD mortality in relation to plasma glucose levels in European men and women (Study IV);
- 5) To estimate the impact of dyslipidaemia on CHD incidence in European men and women with different plasma glucose levels (Study V).

## **4 POPULATIONS AND METHODS**

### **4.1 Study populations**

The DECODE (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe) study was initiated in 1997 and the DECODA (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Asia) study 1998. Briefly, researchers who had carried out population-based or large occupational epidemiological studies on diabetes in Europe or Asia, using a standard 2-h 75-g oral glucose tolerance test (OGTT), were invited to participate. Individual data on fasting plasma glucose (FPG) and 2-h plasma glucose (2hPG) concentrations as well as TC, HDL-C and TG and a number of other variables were sent to the Diabetes Prevention Unit of the National Institute for Health and Welfare in Helsinki, Finland for collaborative data analysis. The Ethics Committee of the National Institute for Health and Welfare had approved the data analysis plans for both the DECODE and the DECODA studies. The two studies consisted of 64 cohorts of mainly population-based from 24 countries and regions around the world, with about 84 000 Europeans and 84 207 Asians of Chinese, Japanese, Indians, Mongolians and Filipinos. The age ranges from 25-99 years. 23 European cohorts and 8 Asian cohorts provide with follow-up data on vital status, comprising 12 283 all-cause deaths and 5811 CVD deaths in Europeans and 1024 and 455 in Asians, respectively. The existing database has been updated continuously.

### **4.2 Inclusion and exclusion criteria**

The inclusion and exclusion criteria for the data analysis of each study are summarized in the Table 2. A total of 19 476 subjects (8960 men and 10 516 women with a mean age of 55 years) from 15 DECODE studies were included in the data analysis for Study I and 19 763 (8933 men and 10 830 women with a mean age of 55 years) from 13 DECODA study cohorts for Study II. Further, 52 355 subjects (24 760 men and 27 595 women with a mean age of 50 years) from 31 (18 in DECODE and 13 in DECODA) study cohorts of 12 countries, representing Asian Indians, Chinese (divided into subgroups of Hong Kong Chinese and Qingdao Chinese), Europeans (divided into subgroups of Central & Northern European and Southern European), Japanese, and Mauritian Indians, met the inclusion criteria for Study III.

Among 14 DECODE cohorts (including 9132 men and 8631 women aged 25-89 years) which provided data on CVD mortality and required covariates for Study IV, 6 (including

4818 men and 4269 women from 4 Finnish and 2 Swedish cohorts) with eligible data on cause-specific morbidity and all variables required were jointly analysed in Study V.

Table 2 Inclusion/Exclusion criteria of the study populations

	Data source	Inclusion criteria	Exclusion criteria
Study I	DECODE	1) Participants aged 35-74 years; 2) Studies including both sexes; 3) Baseline examination performed after 1980; 4) The availability of TC, HDL-C, TG, FPG and 2hPG data	Participants with a prior history of diabetes
Study II	DECODA	1) Participants aged 30-74 years; 2) Studies including both sexes; 3) Baseline examination performed after 1980; 4) The availability of TC, HDL-C, TG, FPG and 2hPG data	Participants with a prior history of diabetes
Study III	DECODE and DECODA	1) Participants aged 25 to 74 years old; 2) Studies including both sexes; 3) Baseline examination performed after 1980; 4) Data on TC, HDL-C, TG, FPG, 2hPG and BMI available	
Study IV	DECODE	1) Cohort study with data on cause-specific mortality; 2) Baseline measurement of TC, HDL-C, TG, FPG, 2hPG, blood pressure and smoking status available	Participants with a prior history of diabetes; Participants lost to the follow-up
Study V	DECODE	1) Cohort study with data on cause-specific morbidity; 2) Baseline measurement of TC, HDL-C, TG, FPG, 2hPG, blood pressure and smoking status available	Participants with either a prior history of diabetes or history of CHD at baseline; Participants lost to the follow-up

### 4.3 Blood lipids and glucose assays

In all cohorts, blood samples were collected after overnight fasting. Plasma glucose was measured in each of the studies with an oxidase or dehydrogenase method. Detailed information on lipids and lipoproteins assays in each study was shown in Appendix 1. Briefly, TC and TG were determined using enzymatic techniques (McGowan et al. 1983; Stein and Steiner 1989; Warnick and Remaley 2001; Dowse et al. 1995; Soderberg et al. 2005) in all and HDL-C measured enzymatically after a precipitation of apoB-containing lipoproteins with established methods (Langlois and Blaton 2006) in most of the laboratories, except in the Qingdao 2006 study from China, the Funagata study from Japan and two Indian studies in India applying direct method for HDL-C assay (Appendix 1).

Non-HDL-C levels were calculated by subtracting HDL-C from TC levels. In Study III, LDL-C was calculated among individuals with a TG value of less than 4.5 mmol/l (n=51,521) using the Friedewald formula (Friedewald et al. 1972) as follows:  $\text{LDL-C (in mmol/l)} = \text{TC} - (\text{HDL-C}) - (0.45 * \text{TG})$ . Individuals with a  $\text{TG} \geq 4.5$  mmol/l (n=834) were excluded from the analysis related to the LDL-C in this sub-study.

#### **4.4 Classification of hyperglycaemia**

According to the WHO 1999 criteria (Alberti and Zimmet 1998), a person with a prior history of diabetes was classified as previously diagnosed diabetes regardless of the glucose levels, and were included only in the data analysis for study III. Those without previously diagnosed diabetes were classified based on either FPG or 2hPG levels. Classification into newly diagnosed diabetes, IGT and normal glucose tolerance (NGT) was determined by 2hPG levels of  $\geq 11.1$ ,  $\geq 7.8 - < 11.1$ , and  $< 7.8$  mmol/l, respectively. FPG levels of  $\geq 7.0$ ,  $\geq 6.1 - < 7.0$ , and  $< 6.1$  mmol/l classified subjects into newly diagnosed diabetes, IFG, and normal fasting glucose (NFG), respectively. According to the both criteria combined, subjects were further classified into: i) normoglycaemia (NFG&NGT), isolated fasting hyperglycaemia ( $\text{FPG} \geq 6.10$  mmol/l and  $2\text{hPG} < 7.80$  mmol/l), isolated post-load hyperglycaemia ( $\text{FPG} < 6.10$  mmol/l and  $2\text{hPG} \geq 7.80$  mmol/l) and combined fasting and post-load hyperglycaemia (CH,  $\text{FPG} \geq 6.10$  mmol/l and  $2\text{hPG} \geq 7.80$  mmol/l) or ii) NFG&NGT, isolated IFG ( $\text{FPG} 6.1-6.9$  mmol/l and  $2\text{hPG} < 7.8$  mmol/l), isolated IGT ( $\text{FPG} < 6.1$  mmol/l and  $2\text{hPG} 7.8-11.0$  mmol/l) and combined IFG and IGT ( $\text{FPG} 6.1-6.9$  mmol/l and  $2\text{hPG} 7.8-11.0$  mmol/l), respectively, for different study objectives.

#### **4.5 Classification of dyslipidaemia**

According to the definition for the metabolic syndrome proposed by the International Diabetes Federation (Alberti et al. 2005), elevated TG was defined as  $\text{TG} \geq 1.7$  mmol/l, and reduced HDL-C was defined as  $\text{HDL-C} < 1.03$  mmol/l for men and  $< 1.29$  mmol/l for women. High LDL-C was defined as  $\text{LDL-C} \geq 3.0$  mmol/l according to the European guidelines on CVD prevention (Graham et al. 2007).

#### **4.6 Definition of fatal and nonfatal cardiovascular events**

Vital status and the date and the cause of death for those deceased were recorded for each subject attending the baseline examination. Subjects who had emigrated and for whom the vital status could not be confirmed were treated as censored at the time of emigration. The International Classification of Diseases (ICD) was used for coding the causes of death.

CVD deaths were defined using ICD codes 401-448 for the eighth or ninth revision and codes I10-I79 for the tenth revision. Participants who died, but for whom information on the causes of death was not available, were considered as missing and were excluded in the calculation of CVD mortality.

Incident CHD events during the follow-up were ascertained through computerized record linkage of the unique national identification numbers of the subjects to the National Death Registry and the National Hospital Discharge Registry in all Finnish and Swedish studies. The ICD was used for coding incident CHD events during the follow up. In the present analysis, we used ICD codes 410-411 for the eighth or ninth revision and code I21 for the tenth revision for the first ever nonfatal MI, and 410-414 and I20-I25 for fatal CHD. Individuals (n=468) with a prior history of CHD before the baseline survey or those (n=41) lost to follow-up were excluded from the data analyses.

## **4.7 Statistical analysis**

### **4.7.1 Cross-sectional studies (Studies I, II and III)**

TG was logarithmically transformed for data analysis because of its skewed distribution. In Studies I and II, the sex-specific mean lipid and lipoprotein concentrations were calculated for subjects of each ethnic group by different glucose categories, adjusted for age and study cohort. Multiple linear regression analysis with standardized coefficient ( $\beta$ ) was used in both Study I and II to examine the relationship between each lipid component (dependent variable) and blood glucose (independent variable) adjusting for age, study cohort, BMI, smoking, and SBP. A  $\chi^2$  test was used for categorical variables. In Study III, we estimated the ethnic- and sex-specific mean concentration of each lipid variable with 95% confidence interval (CI), adjusting for age, study cohort and BMI. Within each glucose category, pairwise comparisons between ethnic groups were made with Bonferroni method to adjust for multiple comparisons. Logistic regression analysis was used to estimate odds of having low HDL-C, high LDL-C or high TG for each ethnic group as compared with that for Central & Northern Europeans (reference group) at a given glucose category, adjusting for age, study cohort, BMI, SBP and smoking status. Waist was not adjusted in the multivariate analysis because it was not available for every study. The proportions of individuals with different dyslipidaemia between ethnicities were compared using  $\chi^2$  test.

### **4.7.2 Prospective studies (Studies IV and V)**

Hazard ratios (HRs) and 95% CIs for CVD mortality (Study IV) or CHD incidence (Study V) in relation to lipids were estimated in each blood glucose category using Cox proportional hazard model analysis for all studies pooled together, with adjustment for age, sex, study cohort, hypertension at baseline, smoking status, waist circumference (BMI in Study V) and lipid parameters.  $\chi^2$  log-likelihood ratio test was applied to determine whether TG or HDL-C (or non-HDL-C) were independent of each other in predicting CHD.

#### **4.7.3 Z-scores**

To reduce the bias derived from differences in methodology between studies, cohort- and sex-specific Z-scores (standard deviation scores) were also calculated for each lipid component (Studies I, II, IV and V) using the formula:  $Z = (X - \mu) / \sigma$ , where X represents the value of the element with mean  $\mu$  and S.D.  $\sigma$  (Rimm AA 1980). Both the original values and the Z-scores of lipid components were analyzed. HRs for CVD mortality or CHD incidence were estimated corresponding to a one unit increase in the Z-scores for each lipid variable. Data were analyzed using SPSS for Windows (version 15.0).



## 5 RESULTS

### 5.1 Blood lipid levels in relation to glucose in Europeans and Asians without a prior history of diabetes (Studies I and II)

Characteristics of study cohorts included in the cross-sectional studies (studies I, II and III) were summarized in the Table 4. In subjects without a prior history of diabetes (study I and II), multivariable adjusted linear regression analyses showed positive associations of FPG with TG [ $\beta$  ranging from 0.06 (average change of 0.06 mmol/l in TG per 1 mmol/l change in FPG,  $p<0.01$ ) for Hong Kong Chinese in men to 0.19 ( $p<0.01$ ) for Asian Indian in men], non-HDL-C, TC/HDL-C and TC in most of the ethnic groups, but an inverse association of FPG with HDL-C in only five groups of women and in Qingdao Chinese men (Table 5). The relationship between lipid and 2hPG (Table 6) followed a similar pattern as that for FPG except for HDL-C (significant change observed in all female groups and in 4 male groups). There were significant interactions between ethnicity and FPG or ethnicity and BMI with regard to each lipid component ( $p<0.05$  for all terms), the interaction term between ethnicity and 2hPG was also significant for HDL-C ( $p<0.05$ ) and TC/HDL-C ( $p<0.05$ ).

The linear regression analyses were repeated in a subgroup of the population having data on fasting insulin and waist, with further adjustment for fasting insulin and/or waist (data not shown). The standardized  $\beta$  coefficient and the model fitness fitted with waist did not differ substantially from that fitted with BMI, but the additional adjustment for fasting insulin attenuated the association between glucose and the lipid profiles and slightly improved the model fitness (the increase in  $R^2$  ranged from 0.01 for HDL-C to 0.03 for TG in men and 0.02 to 0.04 in women), although the  $\beta$  coefficients still remained statistical significance for all sex-specific analyses except for the association between FPG and lipid variable in women.

Table 4 Characteristics of study cohorts included in the studies (Studies I, II and III)

Ethnic group	Study cohort	Year of survey	No.	Mean age (years)	Diabetes (%)		IFG and/or IGT (%)	BMI (kg/m <sup>2</sup> )	TC (mmol/l)	LDL-C <sup>a</sup> (mmol/l)	HDL-C (mmol/l)	TG (mmol/l)
					Undiagnosed	Diagnosed						
Men												
Chinese, Hong Kong, China	HK-wscvdrf <sup>b</sup>	1991	831	38 ± 8	3.7	1.9	8.3	23.3 ± 2.9	5.3 ± 1.0	3.39 ± 0.90	1.25 ± 0.31	1.35 ± 0.88
	HK-cvrfps <sup>c</sup>	1995-1996	1361	46 ± 13	6.8	3.5	15.3	24.3 ± 3.4	5.1 ± 0.9	3.22 ± 0.87	1.16 ± 0.30	1.38 ± 0.87
Chinese, Qingdao, China	Qingdao 2002	2002	697	53 ± 11	11.2	2.0	18.1	26.6 ± 3.4	5.6 ± 1.1	3.34 ± 0.95	1.50 ± 0.28	1.75 ± 1.32
	Qingdao 2006	2006	1614	49 ± 10	13.8	6.9	25.1	25.8 ± 3.2	5.3 ± 1.0	2.99 ± 0.95	1.59 ± 0.44 <sup>d</sup>	1.49 ± 1.13
Asian Indian, India	Chennai 94	1994-1995	255	49 ± 7	11.8	15.3	13.7	22.4 ± 3.9	5.1 ± 1.0	3.09 ± 0.82	1.04 ± 0.25	1.92 ± 1.26
	Chennai 97	1996-1998	397	44 ± 12	6.0	10.3	8.6	22.2 ± 4.1	4.5 ± 1.0	2.82 ± 0.85	0.96 ± 0.22	1.50 ± 1.00
Mauritian Indian, Mauritius	CURES	2003-2004	959	42 ± 11	11.7	8.8	11.1	23.2 ± 3.8	4.7 ± 1.0	2.91 ± 0.86	1.04 ± 0.24 <sup>d</sup>	1.64 ± 1.12
	Chennai 2006	2006	2624	41 ± 11	5.9	11.5	8.3	22.9 ± 4.2	4.3 ± 1.0	2.40 ± 0.78	1.07 ± 0.24 <sup>d</sup>	1.63 ± 1.11
	Mauritius 87	1987	1518	42 ± 12	9.3	5.6	15.3	22.8 ± 3.7	5.6 ± 1.6	3.47 ± 1.46	1.27 ± 0.36	1.83 ± 1.35
	Mauritius 92	1992	846	42 ± 11	9.7	7.7	20.8	24.0 ± 4.8	4.9 ± 0.8	2.90 ± 0.75	1.23 ± 0.33	1.62 ± 1.12
	Mauritius 98	1998	355	43 ± 11	13.0	9.6	15.5	24.5 ± 4.1	5.1 ± 1.1	3.35 ± 0.99	0.90 ± 0.34	1.70 ± 1.00
Japanese, Japan	Funagata	1995-1997	802	56 ± 11	3.2	5.6	12.5	23.6 ± 3.0	5.2 ± 0.9	3.05 ± 0.84	1.41 ± 0.37 <sup>d</sup>	1.53 ± 1.47
	Hisayama	1988	978	55 ± 9	8.1	10.4	23.8	22.9 ± 2.9	5.1 ± 1.0	3.21 ± 1.00	1.26 ± 0.31	1.68 ± 1.49
Italian, Italy	Cremona Study	1990-1991	742	55 ± 8	3.0	8.2	10.5	26.8 ± 3.7	6.0 ± 1.1	3.98 ± 0.97	1.25 ± 0.38	1.67 ± 1.36
Cypriot, Republic of Cyprus	Nicosia Diabetes Study	2003-2004	542	49 ± 12	7.0	11.4	12.0	27.7 ± 4.1	5.5 ± 1.1	3.57 ± 0.95	1.15 ± 0.29	1.78 ± 1.56
Spanish, Spain	The Guia Study	1997	246	52 ± 13	8.5	9.3	19.5	27.5 ± 3.5	5.9 ± 1.1	3.73 ± 0.86	1.23 ± 0.32	1.75 ± 1.09
	The Viva Study	1995-1998	902	49 ± 8	4.2	2.3	13.6	27.6 ± 3.7	5.8 ± 1.1	3.89 ± 0.99	1.19 ± 0.32	1.54 ± 1.10
Finnish, Finland	East-West men	1989	156	71 ± 1	14.1	7.1	28.8	26.3 ± 3.9	5.8 ± 1.1	3.93 ± 0.99	1.16 ± 0.27	1.44 ± 0.65
	National FINRISK STUDY 87, 92	1987-1992	877	54 ± 6	5.9	4.0	25.5	27.7 ± 3.8	6.0 ± 1.0	3.82 ± 0.92	1.24 ± 0.32	1.94 ± 1.24
	National FINRISK Study 2002	2002	1799	58 ± 7	11.1	8.1	34.0	28.0 ± 4.0	5.8 ± 1.1	3.59 ± 0.96	1.34 ± 0.36	1.73 ± 1.08

Polish, Poland Swedish, Sweden	Oulu Study	1992	325	55	22.2	5.8	43.4	26.7±3.4	5.6±1.3	3.82±1.21	1.17±0.33	1.35±0.98
	Savitaipale	1996-1999	584	53±7	7.0	6.5	36.3	26.4±3.9	5.6±1.0	3.56±0.87	1.35±0.36	1.49±1.11
	Vantaa Study	1990-1991	272	65±0.4	4.4	11.4	30.1	26.9±3.7	5.8±1.0	3.83±0.93	1.16±0.30	1.58±0.94
	POLMONICA	1992-1993	168	58±8	8.3	0	32.7	26.5±4.1	5.5±0.9	3.43±0.85	1.39±0.29	1.49±0.98
	MONICA 1986	1986	218	44±11	1.8	11.0	6.9	25.4±3.7	5.9±1.1	4.12±1.00	1.13±0.25	1.41±0.96
	MONICA 1990	1990	364	45±11	1.9	2.7	11.3	25.8±3.3	6.2±1.2	4.14±1.08	1.28±0.31	1.66±1.02
Dutch, The Netherlands	MONICA 1994	1994	497	50±13	3.6	5.4	13.3	27.3±3.7	6.2±1.3	4.12±1.09	1.22±0.30	1.70±1.24
	ULSAM	1991-1995	1176	70±0.6	10.6	5.9	30.5	26.3±3.4	5.8±1.0	3.82±0.88	1.28±0.35	1.45±0.77
	The Hoorn Study	1989-1991	1080	60±6	6.9	3.1	18.5	26.2±3.0	6.4±1.1	4.42±1.02	1.18±0.31	1.68±1.02
British, U.K.	Zutphen	1990	211	71±1	10.4	7.6	24.2	25.9±2.9	6.2±1.1	4.28±1.03	1.15±0.31	1.57±0.87
	ELY	1990-1992	473	54±8	8.2	0	34.2	26.1±3.2	6.5±1.2	4.43±1.05	1.29±0.32	1.49±0.71
	Newcastle Heart Project	1993-1994	376	54±12	8.5	2.7	31.4	26.3±3.9	5.7±1.0	3.61±0.94	1.35±0.39	1.51±0.79
	The Goodinge Study	1990-1991	446	54±10	9.4	0	43.0	25.5±4.1	6.3±1.2	4.17±1.13	1.29±0.38	1.70±1.29
Women												
Chinese, Hong Kong, China	HK-wscvdrf <sup>b</sup>	1991	551	40±8	3.1	2.0	8.7	23.5±3.5	4.8±0.9	2.85±0.82	1.52±0.38	0.89±0.64
	HK-cvrfps <sup>c</sup>	1995-1996	1409	45±12	6.4	4.3	17.3	24.0±3.8	5.0±1.0	3.16±0.91	1.35±0.32	1.09±0.71
Chinese, Qingdao, China	Qingdao 2002	2002	1192	52±11	9.2	2.5	18.0	26.3±3.8	5.7±1.1	3.51±0.91	1.52±0.28	1.48±0.95
	Qingdao 2006	2006	2368	49±10	12.0	7.4	26.7	25.8±3.6	5.3±1.1	3.04±0.92	1.65±0.40 <sup>d</sup>	1.27±0.86
Asian Indian, India	Chennai 94	1994-1995	215	50±8	12.6	19.1	19.5	24.0±4.7	5.4±1.1	3.34±0.91	1.13±0.30	1.82±0.92
	Chennai 97	1996-1998	566	44±13	5.8	6.9	7.8	23.5±4.5	4.7±1.0	2.95±0.88	1.10±0.27	1.30±0.74
	CURES	2003-2004	1116	40±11	9.8	5.1	11.4	23.6±4.0	4.8±1.0	2.93±0.83	1.18±0.25 <sup>d</sup>	1.33±0.80
	Chennai 2006	2006	3250	40±10	5.1	9.2	8.5	23.9±5.0	4.4±1.0	2.52±0.82	1.16±0.25 <sup>d</sup>	1.45±0.88
Mauritian Indian, Mauritius	Mauritius 87	1987	1692	42±13	7.0	4.8	21.4	23.9±4.7	5.3±1.5	3.37±1.39	1.31±0.31	1.29±0.87
	Mauritius 92	1992	960	43±12	8.0	12.2	17.7	25.6±5.2	4.8±0.9	2.84±0.75	1.33±0.29	1.26±0.75
	Mauritius 98	1998	436	42±10	8.7	8.9	18.1	25.2±4.8	4.7±1.1	3.05±0.93	0.99±0.32	1.24±0.62
Japanese, Japan	Funagata	1995-1997	1121	56±11	2.2	3.8	12.7	23.9±3.5	5.4±0.9	3.31±0.86	1.53±0.36 <sup>d</sup>	1.15±0.63
	Hisayama	1988	1312	55±9	4.9	5.6	22.3	23.1±3.2	5.6±1.1	3.69±0.99	1.34±0.29	1.21±0.76
Italian, Italy	Cremona	1990-1991	876	56±8	2.4	5.6	8.3	26.4±4.9	6.2±1.2	4.13±1.10	1.46±0.36	1.25±0.62

Cypriot, Republic of Cyprus	Study Nicosia Diabetes Study	2003-2004	558	50 ± 13	2.5	5.6	12.2	27.0 ± 5.9	5.5 ± 1.0	3.38 ± 0.92	1.48 ± 0.36	1.27 ± 0.89
Spanish, Spain	The Guia Study	1997	322	51 ± 12	4.0	11.2	18.6	28.6 ± 5.4	6.0 ± 1.0	3.91 ± 0.91	1.38 ± 0.33	1.41 ± 0.81
	The Viva Study	1995-1998	1107	49 ± 9	4.2	2.3	13.6	28.2 ± 4.9	5.7 ± 1.1	3.72 ± 0.96	1.40 ± 0.33	1.13 ± 0.61
Finnish, Finland	National FINRISK STUDY 87, 92	1987-1992	1043	54 ± 6	4.0	3.3	14.5	27.2 ± 4.8	5.9 ± 1.1	3.75 ± 0.95	1.50 ± 0.34	1.41 ± 0.90
	National FINRISK Study 2002	2002	2065	57 ± 8	6.2	5.9	23.7	27.9 ± 5.1	5.8 ± 1.0	3.48 ± 0.92	1.65 ± 0.43	1.35 ± 0.72
	Oulu Study	1992	411	55	13.1	2.2	42.8	26.5 ± 4.3	5.9 ± 1.3	3.89 ± 1.29	1.48 ± 0.43	1.05 ± 0.55
	Savitaipale	1996-1999	583	54 ± 7	5.8	4.8	37.9	26.6 ± 4.8	5.7 ± 1.1	3.46 ± 0.93	1.58 ± 0.41	1.26 ± 0.80
	Vantaa Study	1990-1991	337	65 ± 0.4	8.0	8.0	28.2	27.6 ± 4.6	6.3 ± 1.0	4.15 ± 0.99	1.40 ± 0.33	1.53 ± 0.97
Polish, Poland	POLMONICA	1992-1993	190	57 ± 8	5.8	2.6	28.9	29.3 ± 4.9	5.9 ± 1.0	3.69 ± 0.88	1.46 ± 0.26	1.54 ± 0.81
Swedish, Sweden	MONICA 1986	1986	204	44 ± 11	1.1	4.4	9.8	24.4 ± 4.5	6.0 ± 1.3	4.09 ± 1.17	1.38 ± 0.41	1.08 ± 0.67
	MONICA 1990	1990	410	44 ± 11	1.5	1.7	10.5	25.1 ± 4.4	6.1 ± 1.3	3.89 ± 1.19	1.55 ± 0.35	1.33 ± 0.70
	MONICA 1994	1994	521	49 ± 14	4.4	3.6	11.9	25.9 ± 4.7	6.2 ± 1.4	3.96 ± 1.21	1.49 ± 0.40	1.44 ± 0.81
Dutch, The Netherlands	The Hoorn Study	1989-1991	1238	61 ± 6	6.0	3.4	15.3	26.8 ± 4.0	6.9 ± 1.2	4.66 ± 1.10	1.45 ± 0.37	1.55 ± 0.96
British, U.K.	ELY	1990-1992	619	53 ± 8	6.0	0	28.3	25.9 ± 5.0	6.6 ± 1.4	4.39 ± 1.25	1.58 ± 0.38	1.28 ± 0.68
	Newcastle Heart Project	1993-1994	354	53 ± 11	4.8	1.7	23.7	26.4 ± 5.0	5.9 ± 1.2	3.56 ± 1.07	1.61 ± 0.39	1.46 ± 0.78
	The Gooding Study	1990-1991	559	54 ± 10	8.6	0	30.1	26.0 ± 5.3	5.6 ± 1.4	4.31 ± 1.24	1.54 ± 0.40	1.48 ± 0.83

Data are n, means ± S.D, or %.

IFG, impaired fasting glucose; IGT, impaired glucose tolerance; BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides. <sup>a</sup> Calculated only in individuals with TG<4.5mmol/l

<sup>b</sup> Hong Kong Workforce Survey on CVD Risk Factors

<sup>c</sup> Hong Kong Cardiovascular Disease Risk Factor Prevalence Study

Table 5 Age- and study-adjusted mean lipid concentrations by fasting plasma glucose categories (Studies I and II)

Ethnic group	No.	TC				HDL-C				TG				Non-HDL-C (mmol/l)				TC/HDL-C			
		(mmol/l)			Beta*	(mmol/l)			Beta*	(mmol/l)			Beta*				Beta*				Beta*
		NFG	IFG	DM		NFG	IFG	DM		NFG	IFG	DM		NFG	IFG	DM		NFG	IFG	DM	
Men																					
Qingdao Chinese	2033	5.31	5.52 <sup>a</sup>	5.61	0.10 <sup>d</sup>	1.60	1.49 <sup>a</sup>	1.49	-0.09 <sup>d</sup>	1.41	1.87 <sup>a</sup>	2.23	0.19 <sup>d</sup>	3.71	4.03 <sup>a</sup>	4.12	0.14 <sup>d</sup>	3.45	3.79 <sup>a</sup>	3.85	0.17 <sup>d</sup>
Hong Kong Chinese	1837	5.23	5.35	5.26	0.01	1.20	1.10 <sup>a</sup>	1.06	-0.02	1.37	1.68 <sup>a</sup>	1.91	0.06 <sup>c</sup>	4.04	4.25 <sup>a</sup>	4.20	0.01	4.64	5.11 <sup>a</sup>	5.16	0.02
European	8960	5.95	6.10 <sup>a</sup>	6.07	0.06 <sup>d</sup>	1.27	1.26	1.26	-0.02	1.55	1.77 <sup>a</sup>	2.21	0.14 <sup>d</sup>	4.68	4.83 <sup>a</sup>	4.91	0.06 <sup>d</sup>	5.02	5.14 <sup>a</sup>	5.58	0.06 <sup>d</sup>
Japanese	1696	5.10	5.28 <sup>a</sup>	5.25	0.07 <sup>c</sup>	1.34	1.31	1.34	-0.002	1.50	2.02 <sup>a</sup>	2.40	0.12 <sup>b</sup>	3.76	3.97 <sup>a</sup>	3.91	0.07 <sup>b</sup>	4.04	4.33 <sup>a</sup>	4.14	0.06 <sup>b</sup>
Asian Indian	1267	4.71	5.03 <sup>a</sup>	5.10	0.12 <sup>d</sup>	1.03	0.97	0.97	-0.03	1.57	2.01 <sup>a</sup>	2.48	0.19 <sup>b</sup>	3.68	4.05 <sup>a</sup>	4.12	0.13 <sup>d</sup>	4.78	5.35 <sup>a</sup>	5.36	0.10 <sup>d</sup>
Mauritian Indian	2100	5.31	5.51 <sup>a</sup>	5.65	0.06 <sup>c</sup>	1.22	1.20	1.16	-0.01	1.66	2.09 <sup>a</sup>	2.35	0.11 <sup>d</sup>	4.09	4.31 <sup>a</sup>	4.49	0.06 <sup>c</sup>	4.79	4.96	5.43	0.05 <sup>b</sup>
Women																					
Qingdao Chinese	3125	5.40	5.51 <sup>a</sup>	5.81	0.11 <sup>d</sup>	1.64	1.54 <sup>a</sup>	1.57	-0.06 <sup>d</sup>	1.26	1.34 <sup>a</sup>	1.82	0.15 <sup>d</sup>	3.76	3.98 <sup>a</sup>	4.24	0.14 <sup>d</sup>	3.40	3.66 <sup>a</sup>	3.77	0.15 <sup>d</sup>
Hong Kong Chinese	1708	5.00	5.33 <sup>a</sup>	5.26	0.09 <sup>d</sup>	1.41	1.21 <sup>a</sup>	1.30	-0.08 <sup>c</sup>	1.02	1.37 <sup>a</sup>	1.45	0.10 <sup>d</sup>	3.59	4.13 <sup>a</sup>	3.97	0.12 <sup>d</sup>	3.77	4.71 <sup>a</sup>	4.29	0.13 <sup>d</sup>
European	10 516	6.11	6.17	6.20	0.03 <sup>c</sup>	1.54	1.47 <sup>a</sup>	1.36	-0.03 <sup>b</sup>	1.28	1.50 <sup>a</sup>	1.80	0.12 <sup>d</sup>	4.55	4.77 <sup>a</sup>	4.84	0.03 <sup>c</sup>	4.21	4.51 <sup>a</sup>	4.93	0.05 <sup>d</sup>
Japanese	2326	5.46	5.64 <sup>a</sup>	5.75	0.06 <sup>c</sup>	1.44	1.38 <sup>a</sup>	1.33	-0.06 <sup>c</sup>	1.13	1.52 <sup>a</sup>	1.61	0.10 <sup>d</sup>	4.02	4.26 <sup>a</sup>	4.42	0.08 <sup>d</sup>	3.97	4.39 <sup>a</sup>	4.60	0.11 <sup>d</sup>
Asian Indian	1308	4.76	5.06 <sup>a</sup>	5.26	0.16 <sup>d</sup>	1.17	1.03 <sup>a</sup>	1.05	-0.07 <sup>b</sup>	1.28	1.81 <sup>a</sup>	2.11	0.21 <sup>d</sup>	3.59	4.03 <sup>a</sup>	4.21	0.18 <sup>d</sup>	4.24	5.19 <sup>a</sup>	5.13	0.13 <sup>d</sup>
Mauritian Indian	2363	5.05	5.31 <sup>a</sup>	5.83	0.12 <sup>d</sup>	1.27	1.22 <sup>a</sup>	1.18	-0.04	1.22	1.37 <sup>a</sup>	2.05	0.13 <sup>d</sup>	3.78	4.09 <sup>a</sup>	4.65	0.13 <sup>d</sup>	4.21	4.64 <sup>a</sup>	5.33	0.17 <sup>d</sup>

TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; NFG, normal fasting glucose; IFG, impaired fasting glucose; DM, newly diagnosed diabetes classified based on fasting plasma glucose;

\* Standardized coefficients ( $\beta$ ) from multiple linear regression model where lipid as dependent variable and fasting plasma glucose as independent variable, after adjusting for age, cohort, body mass index, systolic blood pressure and smoking status;

<sup>a</sup>  $p < 0.05$  for the difference between IFG and NFG groups;

<sup>b</sup>  $p < 0.05$ , <sup>c</sup>  $p < 0.01$ , <sup>d</sup>  $p < 0.001$  for  $\beta$

Table 6 Age- and study-adjusted mean lipid concentrations by 2-h plasma glucose categories (Studies I and II)

Ethnic group	No.	TC				HDL-C				TG				Non-HDL-C (mmol/l)				TC/HDL-C			
		(mmol/l)				(mmol/l)				(mmol/l)											
		NGT	IGT	DM	Beta*	NGT	IGT	DM	Beta*	NGT	IGT	DM	Beta*	NGT	IGT	DM	Beta*	NGT	IGT	DM	Beta*
Men																					
Qingdao Chinese	2033	5.34	5.38	5.66	0.06 <sup>c</sup>	1.58	1.51 <sup>a</sup>	1.60	-0.01	1.44	1.88 <sup>a</sup>	2.09	0.14 <sup>d</sup>	3.75	3.87 <sup>a</sup>	4.06	0.07 <sup>c</sup>	3.50	3.67 <sup>a</sup>	3.72	0.08 <sup>c</sup>
Hong Kong Chinese	1837	5.21	5.37 <sup>a</sup>	5.29	0.03	1.21	1.12 <sup>a</sup>	1.09	-0.07 <sup>c</sup>	1.30	1.74 <sup>a</sup>	1.90	0.16 <sup>d</sup>	4.01	4.26 <sup>a</sup>	4.20	0.05 <sup>b</sup>	4.58	5.11 <sup>a</sup>	5.12	0.08 <sup>d</sup>
European	8960	5.99	5.91 <sup>a</sup>	6.05	-0.01	1.27	1.21 <sup>a</sup>	1.17	-0.08 <sup>d</sup>	1.56	1.86 <sup>a</sup>	2.27	0.15 <sup>d</sup>	4.72	4.70	4.88	0.02	5.03	5.23 <sup>a</sup>	5.57	0.08 <sup>d</sup>
Japanese	1696	5.09	5.24 <sup>a</sup>	5.29	0.05	1.35	1.27 <sup>a</sup>	1.34	-0.05 <sup>b</sup>	1.45	2.00 <sup>a</sup>	2.46	0.15 <sup>d</sup>	3.74	3.98 <sup>a</sup>	3.96	0.07 <sup>c</sup>	4.01	4.39 <sup>a</sup>	4.24	0.08 <sup>c</sup>
Asian Indian	1267	4.67	5.00 <sup>a</sup>	5.06	0.10 <sup>d</sup>	1.03	1.00	0.97	-0.07 <sup>b</sup>	1.52	1.92 <sup>a</sup>	2.30	0.19 <sup>d</sup>	3.63	3.99 <sup>a</sup>	4.09	0.12 <sup>d</sup>	4.72	5.20 <sup>a</sup>	5.36	0.13 <sup>d</sup>
Mauritian Indian	2100	5.29	5.53 <sup>a</sup>	5.61	0.08 <sup>d</sup>	1.22	1.18 <sup>a</sup>	1.18	-0.01	1.63	2.08 <sup>a</sup>	2.26	0.15 <sup>d</sup>	4.07	4.35 <sup>a</sup>	4.43	0.09 <sup>d</sup>	4.74	5.13 <sup>a</sup>	5.32	0.08 <sup>d</sup>
Women																					
Qingdao Chinese	3125	5.41	5.47	5.76	0.08 <sup>d</sup>	1.63	1.57 <sup>a</sup>	1.58	-0.05 <sup>c</sup>	1.23	1.46 <sup>a</sup>	1.80	0.15 <sup>d</sup>	3.78	3.90 <sup>a</sup>	4.18	0.10 <sup>d</sup>	3.42	3.56 <sup>a</sup>	3.71	0.11 <sup>d</sup>
Hong Kong Chinese	1708	4.96	5.23 <sup>a</sup>	5.25	0.10 <sup>d</sup>	1.43	1.30 <sup>a</sup>	1.19	-0.14 <sup>d</sup>	0.96	1.27 <sup>a</sup>	1.58	0.23 <sup>d</sup>	3.53	3.94 <sup>a</sup>	4.06	0.15 <sup>d</sup>	3.67	4.26 <sup>a</sup>	4.69	0.18 <sup>d</sup>
European	10 516	6.12	6.10	6.11	-0.004	1.51	1.40 <sup>a</sup>	1.27	-0.11 <sup>d</sup>	1.26	1.56 <sup>a</sup>	1.83	0.15 <sup>d</sup>	4.57	4.67 <sup>a</sup>	4.77	0.03 <sup>c</sup>	4.20	4.54 <sup>a</sup>	4.91	0.10 <sup>d</sup>
Japanese	2326	5.44	5.59 <sup>a</sup>	5.73	0.07 <sup>c</sup>	1.45	1.38 <sup>a</sup>	1.31	-0.07 <sup>c</sup>	1.11	1.36 <sup>a</sup>	1.69	0.15 <sup>d</sup>	4.00	4.21 <sup>a</sup>	4.42	0.09 <sup>d</sup>	3.94	4.29 <sup>a</sup>	4.55	0.11 <sup>d</sup>
Asian Indian	1308	4.74	4.96 <sup>a</sup>	5.13	0.15 <sup>d</sup>	1.18	1.10 <sup>a</sup>	1.02	-0.14 <sup>d</sup>	1.23	1.53 <sup>a</sup>	2.05	0.32 <sup>d</sup>	3.55	3.87 <sup>a</sup>	4.11	0.19 <sup>d</sup>	4.16	4.71 <sup>a</sup>	5.17	0.23 <sup>d</sup>
Mauritian Indian	2363	5.04	5.12	5.71	0.11 <sup>d</sup>	1.28	1.22 <sup>a</sup>	1.21	-0.05 <sup>b</sup>	1.17	1.39 <sup>a</sup>	1.88	0.23 <sup>d</sup>	3.76	3.90 <sup>a</sup>	4.51	0.12 <sup>d</sup>	4.18	4.42 <sup>a</sup>	5.14	0.12 <sup>d</sup>

TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; NGT, normal glucose tolerance; IGT, impaired glucose tolerance; DM, newly diagnosed diabetes classified based on 2-h plasma glucose;

\* Standardized coefficients ( $\beta$ ) from multiple linear regression model where lipid as dependent variable and 2-h plasma glucose as independent variable, after adjusting for age, cohort, body mass index, systolic blood pressure and smoking status;

<sup>a</sup>  $p < 0.05$  for the difference between IGT and NGT groups;

<sup>b</sup>  $p < 0.05$ , <sup>c</sup>  $p < 0.01$ , <sup>d</sup>  $p < 0.001$  for  $\beta$

## **5.2 Ethnic differences in lipid profiles by glucose status (Study III)**

### **5.2.1 Lipid distributions in relation to ethnicity and glucose categories**

Age-, cohort- and BMI adjusted mean TC, LDL-C and TG increased while the mean HDL-C decreased with more pronounced glucose intolerance in most of the ethnic groups in individuals without a prior history of diabetes (Fig. 2 a-h). Subjects with undiagnosed diabetes, however, had a worse lipid profile than those with known disease. Within individuals with normoglycaemia, mean lipid and lipoprotein concentrations differed among the ethnic groups. The Europeans had highest TC (Fig. 2 a-b) and LDL-C (Fig. 2 c-d), while Qingdao Chinese had highest HDL-C levels among all ethnic groups (Fig. 2 e-f). In contrast, Asian Indians had the lowest TC (Fig. 2 a-b), LDL-C (Fig. 2 c-d) and HDL-C (Fig. 2 e-f) but the highest TG (Fig. 2 g-h) among the ethnic groups ( $p < 0.05$  for all comparisons). These ethnic differences were consistently found in all glucose categories.

### **5.2.2 Dyslipidaemia in relation to ethnicity by glucose levels**

The multivariate-adjusted odds ratio (95% CI) of having low HDL-C was significantly higher for Asian Indians, Mauritian Indians, Hong Kong Chinese and Southern Europeans but lower for Qingdao Chinese compared with C&N Europeans, across all glucose categories from normal to diabetes (Table 7). Asian Indians and Mauritian Indians tended to have higher but Southern Europeans lower odds ratios for having high-TG compared with the reference group. Unlike that for HDL-C or TG, the odds ratio for having high LDL-C was consistently lower in all Asian ethnic groups compared with the reference, across most of the glucose categories.

In contrast to the lower HDL-C and higher TG profiles, Asian Indians had considerably lower TC and LDL-C concentrations than others. As shown in Table 3, 71% non-diabetic and 57.6% diabetic Asian Indians had low LDL-C ( $< 3.0$  mmol/l), while the corresponding figures were 19.2% and 24.6% ( $p < 0.01$ ) for C&N Europeans and 46.6% and 38.8% ( $p < 0.01$ ) for Qingdao Chinese. However, even within the low LDL-C category, there was still a higher proportion of Asian Indians having low HDL-C compared with others (Table 8). The results were confirmed in the same analysis conducted separately for men and women.

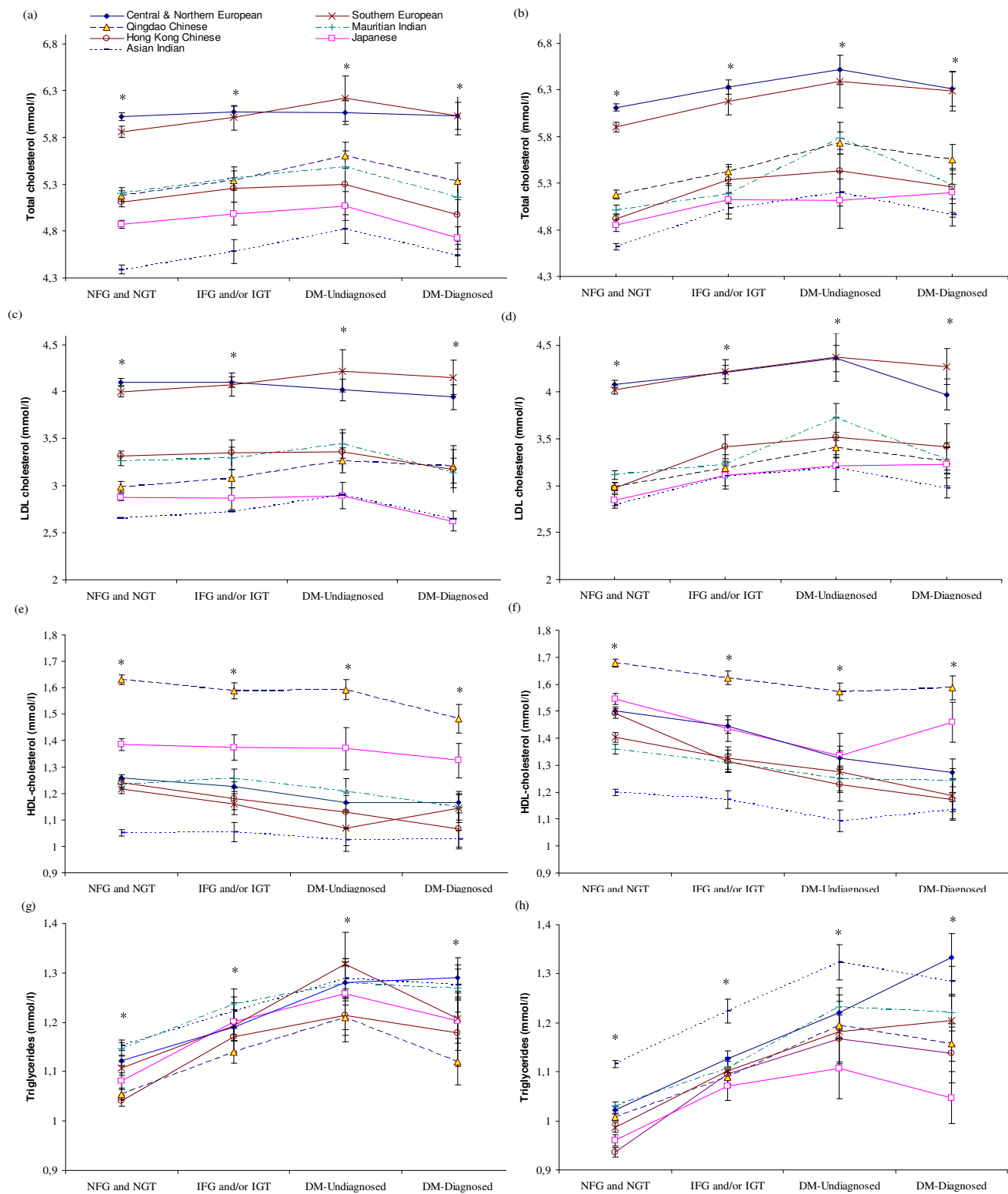


Figure 2 Age-, study cohort- and body mass index-adjusted mean lipid (geometric means for triglycerides) and lipoprotein concentrations and 95% CIs (vertical bars) in men (figure 1-a, c, e and g) and women (figure 1-b, d, f and h) by ethnicities and glucose categories. Abbreviations as in Table 4 and 5. \* p for trend < 0.05 within each glucose category.



Table 7 Odds ratio (95% confidence interval) of having dyslipidaemia in relation to ethnicity by glucose categories (Study III)

	HDL-C < 1.03 in men and < 1.29 in women (mmol/l)				TG ≥ 1.7 mmol/l				LDL-C ≥ 3 mmol/l			
	NFG and NGT	IFG and/or IGT	Undiagnosed diabetes	Diagnosed diabetes	NFG and NGT	IFG and/or IGT	Undiagnosed diabetes	Diagnosed diabetes	NFG and NGT	IFG and/or IGT	Undiagnosed diabetes	Diagnosed diabetes
Men												
Central & Northern European <sup>a</sup>	1	1	1	1	1	1	1	1	1	1	1	1
Hong Kong Chinese	1.63 (1.41-1.87)	2.75 (2.09-3.62)	1.82 (1.20-2.76)	2.57 (1.48-4.46)	0.75 (0.64-0.87)	1.16 (0.88-1.53)	1.05 (0.70-1.58)	0.63 (0.36-1.12)	0.51 (0.44-0.58)	0.61 (0.46-0.82)	0.51 (0.33-0.78)	0.86 (0.49-1.52)
Qingdao Chinese	0.12 (0.09-0.16)	0.07 (0.04-0.13)	0.11 (0.07-0.20)	0.16 (0.08-0.32)	0.68 (0.58-0.79)	0.81 (0.66-1.00)	0.81 (0.61-1.09)	0.40 (0.26-0.63)	0.23 (0.20-0.26)	0.30 (0.24-0.37)	0.44 (0.32-0.60)	0.57 (0.37-0.86)
Asian Indian	4.74 (4.19-5.37)	5.05 (3.88-6.56)	3.07 (2.15-4.40)	2.37 (1.67-3.35)	1.40 (1.23-1.58)	1.53 (1.19-1.97)	1.24 (0.88-1.75)	1.42 (1.01-2.00)	0.12 (0.10-0.13)	0.17 (0.13-0.22)	0.23 (0.16-0.33)	0.29 (0.20-0.41)
Mauritian Indian	1.82 (1.58-2.09)	2.04 (1.58-2.63)	1.27 (0.89-1.81)	1.16 (0.78-1.74)	1.47 (1.28-1.69)	1.55 (1.23-1.98)	1.18 (0.85-1.65)	1.06 (0.72-1.57)	0.39 (0.34-0.45)	0.38 (0.30-0.49)	0.49 (0.34-0.70)	0.75 (0.50-1.12)
Japanese	0.87 (0.73-1.03)	1.29 (0.98-1.70)	0.73 (0.44-1.20)	0.57 (0.36-0.90)	0.99 (0.84-1.15)	1.31 (1.02-1.68)	1.36 (0.88-2.09)	1.02 (0.68-1.53)	0.26 (0.23-0.30)	0.35 (0.27-0.44)	0.36 (0.23-0.57)	0.77 (0.51-1.16)
Southern European Women	1.21 (1.06-1.37)	1.49 (1.15-1.93)	1.79 (1.19-2.70)	1.13 (0.78-1.63)	0.78 (0.69-0.88)	0.83 (0.65-1.07)	1.16 (0.77-1.75)	0.58 (0.40-0.84)	0.87 (0.75-1.00)	0.99 (0.73-1.36)	1.80 (1.01-3.23)	1.52 (0.99-2.31)
Women												
Central & Northern European <sup>a</sup>	1	1	1	1	1	1	1	1	1	1	1	1
Hong Kong Chinese	2.23 (1.93-2.57)	3.79 (2.88-4.98)	3.02 (1.88-4.85)	3.03 (1.68-5.48)	0.86 (0.69-1.08)	1.16 (0.85-1.58)	0.98 (0.61-1.57)	0.69 (0.39-1.21)	0.41 (0.35-0.47)	0.64 (0.48-0.86)	0.61 (0.36-1.04)	1.21 (0.66-2.22)
Qingdao Chinese	0.66 (0.57-0.76)	0.52 (0.41-0.65)	0.27 (0.19-0.38)	0.20 (0.13-0.31)	1.29 (1.11-1.50)	1.06 (0.87-1.30)	0.99 (0.73-1.36)	0.57 (0.39-0.84)	0.40 (0.36-0.45)	0.45 (0.37-0.55)	0.48 (0.33-0.69)	0.67 (0.45-0.99)
Asian Indian	10.91 (9.68-12.30)	7.80 (5.99-9.94)	8.64 (5.62-13.29)	4.34 (2.93-6.44)	2.76 (2.39-3.18)	2.21 (1.71-2.87)	3.13 (2.15-4.55)	1.29 (0.90-1.85)	0.22 (0.20-0.25)	0.36 (0.28-0.47)	0.36 (0.24-0.54)	0.41 (0.28-0.60)
Mauritian Indian	4.41 (3.88-5.02)	3.80 (3.05-4.74)	2.65 (1.82-3.88)	2.26 (1.53-3.35)	1.38 (1.16-1.65)	1.15 (0.91-1.47)	1.54 (1.07-2.23)	0.81 (0.56-1.19)	0.48 (0.42-0.55)	0.50 (0.40-0.63)	0.78 (0.51-1.21)	0.85 (0.57-1.27)
Japanese	2.40 (2.12-2.73)	3.07 (2.44-3.87)	2.65 (1.62-4.34)	1.07 (0.67-1.72)	0.92 (0.77-1.09)	1.19 (0.93-1.53)	0.72 (0.43-1.21)	0.41 (0.25-0.68)	0.58 (0.51-0.66)	0.67 (0.52-0.87)	0.56 (0.31-0.99)	2.24 (1.27-3.93)
Southern European	1.50 (1.34-1.68)	1.62 (1.26-2.08)	0.93 (0.56-1.52)	1.70 (1.13-2.56)	0.70 (0.60-0.81)	0.80 (0.61-1.05)	0.60 (0.36-1.01)	0.53 (0.35-0.79)	0.98 (0.87-1.11)	1.39 (1.01-1.93)	1.38 (0.70-2.72)	2.67 (1.62-4.42)

Model adjusted for age, study cohort, body mass index, systolic blood pressure and smoking status.

NFG, normal fasting glucose; NGT, normal glucose tolerance; other abbreviations as in Table 4.

<sup>a</sup> Reference group

Table 8 Proportions (%) of individuals according to lipid levels stratified by diabetic status in each ethnic group (Study III)

	LDL-C < 3 mmol/l				LDL-C ≥ 3 mmol/l			
	Normal HDL-C	Low HDL-C	High TG <sup>b</sup>	both, %	Normal HDL-C	Low HDL-C <sup>a</sup>	High TG <sup>b</sup>	both, %
	and normal TG, %	C <sup>a</sup> alone, %	alone, %		and normal TG, %	alone, %	alone, %	
Non-diabetic population								
Hong Kong Chinese	29.3	9.9	1.6	4.2	32.1	12.9	3.7	6.2
Qingdao Chinese	31.0	5.4	8.3	1.9	40.5	2.4	9.8	0.7
Asian Indian	23.2	33.6	3.2	11.0	9.2	10.7	2.8	6.4
Mauritian Indian	23.9	15.8	5.0	4.7	23.2	14.7	5.7	7.0
Japanese	25.2	6.4	3.4	3.5	38.2	13.0	5.0	5.3
Central & Northern European	13.3	2.3	2.0	1.6	48.6	9.7	12.6	10.0
Southern European	14.2	4.3	1.1	2.1	45.5	15.1	7.8	10.0
Diabetic population								
Hong Kong Chinese	12.4	9.6	1.4	11.0	22.6	18.1	7.6	17.2
Qingdao Chinese	21.1	3.5	11.1	3.1	37.9	2.7	19.1	1.5
Asian Indian	12.8	17.4	6.0	21.4	8.1	12.4	7.2	14.7
Mauritian Indian	12.4	8.6	6.4	10.2	21.2	15.5	10.2	15.5
Japanese	14.3	6.0	7.1	5.1	34.3	11.6	12.2	9.4
Central & Northern European	10.5	2.8	4.9	6.4	30.4	9.3	16.4	19.4
Southern European	7.5	3.3	6.0	10.2	24.4	11.2	12.8	14.8

Abbreviations as in Table 4.

<sup>a</sup> < 1.03 mmol/l in men and < 1.29 mmol/l in women

<sup>b</sup> ≥ 1.70 mmol/l

### **5.3 Dyslipidaemia and CVD mortality in the Europeans without a prior history of diabetes (Study IV)**

Among the 17 763 European subjects of 14 cohorts, 1286 (7.2%) were identified as having newly diagnosed diabetes at baseline examination, 2690 (15.1%) IFG, 2557 (14.4%) IGT, and 4390 (24.7%) IFG and/or IGT. During an average of 10 years of follow-up, there were 861 deaths (686 men and 185 women) from CVD accumulated (Table 9).

Multivariate-adjusted Cox proportional hazards analysis showed that, HDL-C was inversely associated with CVD death in all glucose categories except for IGT (Table 10) or isolated post-load hyperglycaemia (Table 11). TG was positively associated with CVD death only in those with newly diagnosed diabetes or CH. Non-HDL-C and TC/HDL-C were significantly associated with increased risk of CVD death in subjects with IFG (Table 10) as well as in those with isolated fasting hyperglycaemia (Table 11), but none of these lipid variables significantly predicted CVD death in individuals with IGT (Table 10) or in those with isolated post-load hyperglycaemia (Table 11). No significant interaction between lipid and glucose was observed in any group. Due to the relatively low number of deaths from CVD in women, gender-specific analyses were only able to do in men and results for men were not different from the combined data analysis.

Table 9 Baseline characteristics of subjects and number of deaths from cardiovascular disease during follow-up (Study IV)

Countries and Studies	No. (men/women)	Mean age in years (range)	IFG (%)	IGT (%)	Diabetes (%)	Hypertension (%)	Current Smoking (%)	Follow-up year (Max)	No. of CVD Deaths (men/women)
Finland									
East-West men	354/-	76 (69-89)	15.8	27.1	12.7	81.9	14.1	17.1	137/-
National FINRISK Study 87, 92	841/1007	54 (44-64)	13.6	11.1	5.1	64.5	20.6	15.0	54/18
National FINRISK Study 2002	1640/1934	57 (45-74)	20.3	16.8	8.7	64.6	28.3	4.9	22/5
Oulu Study	304/401	55 (55-55)	30.6	28.7	17.6	71.3	23.3	15.0	13/7
Vantaa Study	240/308	65 (64-66)	10.8	27.9	6.6	80.7	16.6	13.9	29/10
Italy									
Cremona Study	731/927	57 (40-88)	4.4	8.7	3.4	58.7	22.7	15.7	76/65
Poland									
POLMONICA	163/181	57 (43-73)	13.7	22.7	7.3	47.4	25.6	6.6	13/2
Sweden									
MONICA	993/1077	46 (25-74)	5.5	7.2	2.5	32.1	21.6	20.6	36/19
ULSAM	1095/-	70 (69-73)	9.3	28.4	11.1	73.9	20.8	12.4	119/-
The Netherlands									
The Hoorn Study	1081/1269	61 (49-77)	10.9	9.5	6.9	49.4	33.7	10.2	66/32
Zutphen Study	442/-	75 (69-89)	17.9	10.0	10.6	67.4	22.6	4.8	46/-
U.K.									
Isle of ELY Diabetes Project	425/599	54 (40-69)	22.7	15.4	6.6	32.5	16.8	15.7	22/6
Newcastle Heart Project	375/360	54 (30-76)	21.2	13.3	7.2	34.6	28.0	10.6	25/8
The Goodinge Study	448/568	54 (39-76)	31.9	9.3	8.9	21.9	37.7	9.7	28/13
Total	9132/8631	57 (25-89)	15.1	14.4	7.2	54.1	25.3	20.6	686/185

Abbreviations as in Table 4.

Table 10 Number of subjects and percentage of deaths from cardiovascular disease, and multivariate-adjusted hazard ratios (95% CIs) for cardiovascular mortality corresponding to a one unit increase in the Z-score for lipid according to fasting or 2-hour glucose criteria in subjects without a prior history of diabetes (Study IV)

	FPG (mmol/l) category		2hPG (mmol/l) category		New-DM (FPG $\geq$ 7.80 and/or 2hPG $\geq$ 11.10mmol/l)
	NFG (<6.10)	IFG (6.10-6.99)	NGT (<7.80)	IGT (7.80-11.09)	
No.	13 787	2690	13 920	2557	1286
CVD death (%)	4.4	5.5	4.1	7.4	9.2
HDL-C <sup>a</sup>	0.88 (0.80-0.98)	0.66 (0.50-0.87)	0.83 (0.74-0.92)	0.96 (0.79-1.16)	0.68 (0.52-0.88)
TG <sup>a</sup>	1.03 (0.92-1.15)	1.09 (0.88-1.34)	1.05 (0.93-1.19)	1.00 (0.83-1.19)	1.12 (1.01-1.28)
TC <sup>b</sup>	0.96 (0.87-1.06)	1.10 (0.88-1.37)	1.01 (0.91-1.12)	0.92 (0.77-1.11)	1.05 (0.83-1.31)
Non-HDL-C <sup>b</sup>	1.01 (0.91-1.11)	1.20 (1.00-1.50)	1.07 (0.97-1.19)	0.94 (0.78-1.13)	1.17 (0.93-1.46)
TC/HDL-C <sup>b</sup>	1.09 (0.99-1.20)	1.36 (1.11-1.67)	1.18 (1.07-1.31)	1.01 (0.85-1.09)	1.26 (1.04-1.53)

<sup>a</sup> Adjusted for age, sex, cohort, hypertension, smoking status, waist circumference and total cholesterol

<sup>b</sup> Adjusted for age, sex, cohort, hypertension, smoking status and waist circumference

Table 11 Number of subjects and percentage of deaths from cardiovascular disease, and multivariate-adjusted hazard ratios (95% CIs) for cardiovascular mortality corresponding to a one unit increase in the Z-score for lipid according to both fasting and 2-hour glucose criteria in subjects without a prior history of diabetes (Study IV)

FPG (mmol/l)	<6.10	$\geq$ 6.10	<6.10	$\geq$ 6.10
2hPG (mmol/l)	<7.80	<7.80	$\geq$ 7.80	$\geq$ 7.80
No.	12 087	2048	1896	1732
CVD death (%)	4.0	4.7	7.5	8.7
HDL-C <sup>a</sup>	0.84 (0.75-0.94)	0.66 (0.48-0.92)	1.03 (0.84-1.27)	0.67 (0.51-0.89)
TG <sup>a</sup>	1.05 (0.92-1.20)	1.10 (0.85-1.44)	0.95 (0.75-1.19)	1.12 (1.00-1.27)
TC <sup>b</sup>	0.97 (0.87-1.08)	1.29 (0.99-1.68)	0.91 (0.74-1.12)	1.02 (0.83-1.25)
Non-HDL-C <sup>b</sup>	1.03 (0.92-1.15)	1.40 (1.08-1.81)	0.91 (0.73-1.12)	1.11 (0.90-1.36)
TC/HDL-C <sup>b</sup>	1.14 (1.03-1.27)	1.44 (1.13-1.84)	0.94 (0.77-1.15)	1.26 (1.05-1.50)

<sup>a</sup> Adjusted for age, sex, cohort, hypertension, smoking status, waist circumference and total cholesterol

<sup>b</sup> Adjusted for age, sex, cohort, hypertension, smoking status and waist circumference

## 5.4 Dyslipidaemia and CHD incidence in the Europeans without a prior history of diabetes (Study V)

Among the 9087 subjects of 6 European cohorts who were free of CHD at baseline, 622 (6.8%) were identified as having diabetes, 979 (10.8%) isolated IGT, 797 (8.8%) isolated IFG, and 429 (4.7%) had combined IFG and IGT. During a median follow-up of 10.2 years, a total of 457 incident CHD cases (379 men and 78 women) were identified (Table 12).

Table 12 Demographic and follow-up information of the participants (Study V)

Studies	No. (men/ women)	Mean age, years	Prevalence (%)				Median of follow-up, years	No. of incident CHD (men/women)
			Diabetes	Isolated IGT	Isolated IFG	Combined IFG and IGT		
Finland								
East-West men	295/-	76	13.2	19.7	7.1	8.5	8.0	85/-
National	789/990	53	4.8	6.5	9.0	4.2	14.9	61/22
FINRISK								
Study 87, 92								
National	1536/1909	58	8.6	10.0	13.8	6.3	4.8	26/17
FINRISK								
Study 2002								
Vantaa Study	212/296	65	6.3	20.9	4.1	6.5	13.3	31/21
Sweden								
MONICA	959/1074	46	2.6	5.8	3.8	1.4	15.8	58/18
ULSAM	1027/-	70	11.6	23.0	3.9	5.1	9.9	118/-
Total	9087	57	6.8	10.8	8.8	4.7	10.2	379/78

Abbreviations as in Table 4.

Individuals with hyperglycaemia (isolated IFG, isolated IGT, combined IFG and IGT, or diabetes) were older and had worse lipid profiles, higher BMI and waist circumference and the higher prevalence of hypertension than those with normoglycaemia (Table 13). In general, individuals with IFG and/or IGT had the CVD risk factor profiles falling between that observed in the normoglycaemic and diabetic people. In addition, individuals with combined IFG and IGT had comparable BMI and prevalence of hypertension with diabetic patients.

Table 13 Baseline characteristics of subjects with different glucose categories defined by fasting and 2-h plasma glucose (Study V)

	NFG and NGT	Isolated IFG	Isolated IGT	Combined IFG and IGT	Diabetes
No.	6260	797	979	429	622
Men (%)	48.5	69.6	55.6	63.2	66.6
Age (years)	55±0.1	57±0.4 <sup>a</sup>	62±0.3 <sup>a</sup>	61±0.5 <sup>a</sup>	62±0.4 <sup>a</sup>
BMI (kg/m <sup>2</sup> )	26.2±0.1	28.0±0.1 <sup>a</sup>	27.4±0.1 <sup>a</sup>	29.4±0.2 <sup>a</sup>	29.5±0.2 <sup>a</sup>
Waist (cm)	88.4±0.1	93.4±0.4 <sup>a</sup>	92.3±0.4 <sup>a</sup>	97.5±0.6 <sup>a</sup>	98.2±0.5 <sup>a</sup>
TC (mmol/l)	5.93±0.01	6.03±0.04 <sup>b</sup>	5.88±0.04	5.89±0.05	5.96±0.04
TG (mmol/l)	1.36±0.01	1.61±0.03 <sup>a</sup>	1.62±0.03 <sup>a</sup>	1.83±0.04 <sup>a</sup>	1.97±0.03 <sup>a</sup>
HDL-C (mmol/l)	1.45±0.01	1.41±0.01 <sup>a</sup>	1.36±0.01 <sup>a</sup>	1.30±0.02 <sup>a</sup>	1.28±0.02 <sup>a</sup>
Non-HDL-C (mmol/l)	4.48±0.01	4.61±0.04 <sup>a</sup>	4.52±0.04	4.59±0.05	4.68±0.05 <sup>a</sup>
TC/HDL-C	4.38±0.02	4.56±0.05 <sup>a</sup>	4.60±0.04 <sup>a</sup>	4.81±0.07 <sup>a</sup>	4.95±0.05 <sup>a</sup>
Hypertension (%)	52.1	69.8 <sup>a</sup>	73.4 <sup>a</sup>	81.4 <sup>a</sup>	82.4 <sup>a</sup>
Smoking (%)	23.4	30.4 <sup>a</sup>	19.1 <sup>a</sup>	20.1	22.5

Data are age-, sex- and cohort-adjusted means ± SE, or %; NFG, normal fasting glucose; NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; TC, total cholesterol; Non-HDL-C, non-HDL cholesterol

<sup>a</sup> P<0.01 compared with NFG and NGT

<sup>b</sup> P<0.05 compared with NFG and NGT

In individuals with normoglycaemia each lipid variable was associated with incident CHD events; the age-, sex-, and cohort-adjusted HRs (95% CIs) were 1.22 (1.08-1.38), 0.71 (0.62-0.82), 1.35 (1.20-1.53), 1.42 (1.29-1.58) and 1.23 (1.09-1.39) for TC, HDL-C, non-HDL-C, TC/HDL-C and TG, respectively (Table 14). Similarly in people with diabetes, TC, non-HDL-C and TC/HDL-C and TG were directly associated while HDL-C inversely associated with CHD risk. In contrast, none of these was significant in people with isolated IGT or with combined IFG and IGT, and only TC and non-HDL-C predicted incident CHD in those with isolated IFG.

After multivariate adjustment for known non-lipid risk factors (Table 14), the results remained significant in normoglycaemic and diabetic groups. Further addition of HDL-C or non-HDL-C to the model with TG improved the model prediction in the diabetic individuals ( $\chi^2 = 6.13$  for HDL-C, 1 df,  $p < 0.05$  or  $\chi^2 = 6.64$  for non-HDL-C, 1 df,  $p < 0.05$ ). TG also improved the prediction of the model with HDL-C ( $\chi^2 = 3.90$  for TG, 1 df,  $p < 0.05$ ), but did not contribute to the prediction in the model with non-HDL-C ( $\chi^2 = 2.54$  for TG, 1 df,  $p > 0.05$ ). Since TG was not a significant predictor of the CHD in other non-diabetic glycaemic groups, the log-likelihood ratio test was not performed in other groups. No interaction was observed for the term of TG\*HDL-C\*glucose category ( $\chi^2 = 2.35$ , 4 df,  $p > 0.05$ ) or TG\*non-HDL-C\*glucose category ( $\chi^2 = 3.68$ , 4 df,  $p > 0.05$ ). We reported results from multivariate Cox regression analysis by pooling men and women together because sex-specific analysis for women was not allowed due to a low number of cases. There was no significant interaction between sex and each lipid component except for HDL-C in the normoglycaemic group ( $\chi^2 = 5.33$ , 1 df,  $p < 0.05$ ).



Table 14 Multivariate-adjusted hazard ratios (95% CIs) for coronary heart disease morbidity corresponding to a one unit increase in the Z-score for each lipid according to fasting and 2-h plasma glucose criteria in people without a prior history of diabetes (Study V)

	NFG and NGT	Isolated IFG	Isolated IGT	Combined IFG and IGT	Diabetes
No.	6260	797	979	429	622
No. of Incident CHD					
(rate per 1,000 person-year)	254 (3.8)	37 (5.8)	74 (8.4)	30 (8.7)	62 (13.0)
Age-, sex- and cohort-adjusted model					
TC	1.22 (1.08-1.38)	1.46 (1.06-2.00)	1.13 (0.89-1.45)	1.35 (0.89-2.06)	1.31 (1.03-1.67)
TG	1.23 (1.09-1.39)	1.07 (0.76-1.49)	1.04 (0.84-1.29)	1.11 (0.82-1.51)	1.18 (1.05-1.33)
HDL-C	0.71 (0.62-0.82)	1.29 (0.90-1.85)	1.06 (0.82-1.38)	0.98 (0.63-1.52)	0.64 (0.45-0.91)
Non-HDL-C	1.35 (1.20-1.53)	1.39 (1.01-1.93)	1.11 (0.88-1.41)	1.35 (0.90-2.04)	1.43 (1.13-1.83)
TC/HDL-C	1.42 (1.29-1.58)	1.13 (0.81-1.59)	1.04 (0.83-1.32)	1.02 (0.71-1.46)	1.54 (1.22-1.95)
Multivariate-adjusted model <sup>a</sup>					
TC	1.21 (1.06-1.37)	1.53 (1.10-2.15)	1.03 (0.80-1.34)	1.42 (0.90-2.27)	1.39 (1.08-1.80)
TG	1.14 (0.99-1.30)	1.09 (0.78-1.52)	0.98 (0.78-1.22)	1.07 (0.76-1.49)	1.21 (1.07-1.37)
HDL-C	0.76 (0.66-0.87)	1.32 (0.91-1.93)	1.05 (0.81-1.38)	1.05 (0.64-1.73)	0.57 (0.39-0.84)
Non-HDL-C	1.31 (1.16-1.49)	1.47 (1.05-2.08)	1.02 (0.80-1.31)	1.39 (0.88-2.19)	1.56 (1.21-2.01)
TC/HDL-C	1.36 (1.22-1.53)	1.18 (0.83-1.69)	0.98 (0.77-1.25)	0.97 (0.65-1.45)	1.74 (1.34-2.26)
Mutually adjusted model 1 <sup>a</sup>					
TG	1.02 (0.88-1.19)	1.18 (0.83-1.67)	0.99 (0.78-1.26)	1.11 (0.76-1.62)	1.16 (1.01-1.33)
HDL-C	0.76 (0.66-0.89)	1.38 (0.94-2.03)	1.05 (0.79-1.40)	1.13 (0.65-1.98)	0.62 (0.42-0.92)
Mutually adjusted model 2 <sup>a</sup>					
TG	1.02 (0.87-1.19)	0.89 (0.58-1.36)	0.95 (0.73-1.25)	0.91 (0.61-1.32)	1.14 (0.99-1.32)
Non-HDL-C	1.31 (1.14-1.49)	1.56 (1.05-2.32)	1.05 (0.78-1.42)	1.50 (0.86-2.65)	1.44 (1.10-1.90)

Abbreviations as in Table 13.

<sup>a</sup> Adjusted for age, sex, cohort, body mass index, hypertension status and smoking status

## 6 DISCUSSION

### 6.1 Relationship between lipids and lipoproteins and glucose

It is well established that lipid profiles are worse in diabetic than in non-diabetic individuals (Barrett-Connor et al. 1982; Wilson 1994; Betteridge 1999). Our study in the Europeans (Study I) and Asians (Study II), along with others (Harris et al. 2002; Novoa et al. 2005; Chen et al. 2006; Pankow et al. 2007), indicated that subjects with IFG/IGT were also associated with a poor lipid profile compared with those with NFG/NGT. With worsening glucose tolerance, levels of TG and TC/HDL-C markedly deteriorated in both sexes. TG, non-HDL-C and TC/HDL-C were positively associated with FPG or 2hPG in subjects without a prior history of diabetes. An inverse relationship between HDL-C and glucose was more pronounced for 2hPG than for FPG. The association of glucose with TC was not as clear as that with TG. This may be due to the different compositional changes in LDL particles in the hyperglycaemic states. VLDL-C and IDL-C levels are higher, whereas HDL-C levels are lower in diabetic than in non-diabetic individuals. Despite the increased risk of CHD in diabetes, LDL-C concentrations are often similar to those of control subjects (Howard 1999). TC, finally, is the sum of VLDL-C, IDL-C, LDL and HDL-C.

The diabetic dyslipidaemia may be the exhibition of the underlying insulin resistance, a central pathophysiological feature of type 2 diabetes. Insulin resistance appears to cause hyperinsulinaemia, enhanced hepatic gluconeogenesis and glucose output, reduced suppression of lipolysis in adipose tissue leading to a high FFA flux and increased hepatic VLDL secretion causing hypertriglyceridaemia and reduced levels of HDL-C (Avramoglu et al. 2006). Individuals with IGT have been reported having more atherogenic lipid profiles, with higher TG and lower HDL-C levels than those with NGT or IFG (Blake et al. 2004; Wasada et al. 2004). The association of 2hPG with HDL-C compared with that of FPG with HDL-C, along with current evidence suggests that IFG and IGT may have different pathophysiologies (Bock et al. 2006) and different clinical consequences (The DECODE Study Group 2001). Subjects with IFG have severe hepatic insulin resistance and normal or nearly-normal muscle insulin sensitivity combined with impairment in first-phase insulin release, while people with IGT have marked muscle insulin resistance but only mild hepatic insulin resistance combined with impairment in first- and second-phase insulin release (Blake et al. 2004; Abdul-Ghani et al. 2006; Meyer et al. 2006). This implies that IGT is more closely related to insulin resistance than IFG (Wasada et al. 2004). In contrast with men, women with IFG were associated with worse HDL-C levels than were women with NFG in our study. A recent study has also shown an inverse relationship between FPG and

HDL-C in a Chinese population older than 50 years consisting of over 70% of female participants (Thomas et al. 2006). Further studies are needed on the issue whether gender difference in insulin resistance exists for the given range of glucose.

Insulin resistance as well as abdominal obesity has been considered underlying cause of hyperglycaemia. Each of them is feature of the metabolic syndrome and plays an important role in lipid and glucose metabolism (Thomas et al. 2004; Katzmarzyk et al. 2006; Onat et al. 2007). This raises the question that to what extent is the relationship between lipid and blood glucose mediated through insulin resistance or abdominal obesity. We also carried out the regression analyses with further adjustment for fasting insulin levels and waist in both European and Asian populations. The consistent results suggest that the relationship between glucose and the lipid profiles, to some extent, is mediated through fasting insulin levels, a surrogate indicator of the insulin resistance, but the association could not be fully explained by fasting insulin levels.

## **6.2 Distinct ethnic differences in lipid profiles across glucose categories**

In the collaborative analysis of seven ethnic groups of European and Asian populations (Study III), considerable ethnic differences in lipid profiles were observed within each glucose category. Asian Indians exhibited an adverse lipid pattern consisting of low HDL-C and high TG across all glucose categories as compared with other ethnic groups. Reduced HDL-C is prevalent even in Asian Indians with desirable LDL-C levels regardless of the diabetic status. In addition, in most of the ethnic groups, individuals detected with undiagnosed diabetes had a worse lipid profile than did diagnosed cases.

The ethnic differences in lipid profiles given the same glucose levels have not been well investigated. In the HeartSCORE and IndiaSCORE studies (Mulukutla et al. 2008) where lipids were measured with the same assay procedures for Asian Indians as for whites and blacks, Asian Indians had lowest TC and HDL-C and highest TG among all the ethnic groups studied. In another multi-ethnic study of the 1992 Singapore National Health Survey (Tan et al. 1999), Asian Indians appeared to have lower HDL-C but higher TG levels compared with Chinese. The findings of these previous studies are consistent with ours although glucose status was not controlled in the previous studies. The causes of ethnic difference in cardiovascular risk profile are complex. Possible contributors include genetic, environmental, psychosocial, cultural and unmeasured factors and many are not well clarified (Zaninotto et al. 2007). It is clear that the observed ethnic differences in lipid profiles cannot be explained by genetics alone and may be more indicative of lifestyle-

related factors such as dietary pattern and physical activity (Ruixing et al. 2008; McNaughton et al. 2009; Sisson et al. 2009). To what extent is ethnic-specific lifestyle pattern associated with different lipid profiles deserves further investigation. An adverse lipid profile in Asian Indians has been reported to be associated with the greater susceptibility to insulin resistance (Tan et al. 1999; Anand et al. 2000; Bhalodkar et al. 2005; Palaniappan et al. 2007), and a higher percentage of body fat for the same BMI as compared with whites (McKeigue et al. 1991), which may contribute to the high prevalence of CVD (Kuller 2004) and diabetes (Ramachandran et al. 2008; Snehalatha and Ramachandran 2009) in this ethnic group. In addition, it may also reflect the genetic variation, for example, at the apoE locus (Tan et al. 2003) and an excess of other risk factors such as homocysteine, Lp(a) or dietary fat (France et al. 2003). The difference in HDL-C concentrations between Qingdao and Hong Kong Chinese subgroups cannot be simply explained by the difference in assay methods. It may largely attribute to the differences in dietary structure and preference, geographic and environmental factors. Shellfish and beer, for example, are commonly consumed all the year round in Qingdao. Nevertheless, whether other factors exist and contribute to the high HDL-C in Qingdao needs to be further investigated.

Similar to others (Harris and Eastman 2000; Hadaegh et al. 2008), we observed a worse lipid profile in individuals with undiagnosed diabetes than that of previously diagnosed patients in most of the ethnic groups, indicating individuals with undiagnosed diabetes are at increased CVD risk and need to be identified and treated early. On the other hand, glycaemic control is shown to be an important determinant of diabetic dyslipidaemia (Ismail et al. 2001). The better lipid profile in diagnosed diabetes as compared with undiagnosed diabetes might imply a benefit of lifestyle intervention or drug treatment targeting favorable metabolic profiles and hemoglobin A1c (HbA1c), a surrogate measure for average blood glucose. However, to what extent the levels of HbA1c have contributed to the differences is unknown due to the lack of information in the current study. In addition, the data on lipid-lowering treatment is not available for most of the earlier studies conducted in the 1990s because the statins were not widely prescribed at that time. These deserve further investigation in future studies.

### **6.3 Lipids and lipoproteins and cardiovascular mortality**

The Study IV, which carried out in European men and women without a prior history of diabetes, showed that the low HDL-C and the high TC/HDL-C increased the risk of death from CVD independent of the fasting hyperglycaemia, but the relationship was not observed in the presence of isolated post-load hyperglycaemia (or IGT). Non-HDL-C was

also able to predict CVD death only in the presence of fasting hyperglycaemia and TG only in the most advanced stage of prediabetes, i.e., CH, and in newly diagnosed diabetes.

Our findings on the HDL-C and TC/HDL-C were consistent with previous reports in either diabetic patients (Wilson et al. 1988; Laakso 1996; Boden 2000; Hu et al. 2002) or non-diabetic subjects (Kinosian et al. 1994; Criqui and Golomb 1998; Schulze et al. 2004; Wang et al. 2007) where diabetes or pre-diabetic status were defined based on either fasting alone (Liu et al. 2005) or on both fasting and post-load glucose criteria, but did not distinguish the isolated fasting from the isolated post-load hyperglycaemic categories. The finding that non-HDL-C predicted CVD death only in individuals with isolated fasting hyperglycaemia or IFG could be explained by the potential significance of postprandial hyperlipidaemia in IFG, which is characterized by severe hepatic insulin resistance with normal or near-normal muscle insulin sensitivity (Abdul-Ghani et al. 2006). Since non-HDL-C is the sum of VLDL-C, IDL-C and LDL-C; and VLDL-C (i.e., TG) and LDL-C (i.e., TC) were not significantly associated with CVD death in IFG, it could be speculated that the association of non-HDL-C with CVD death in IFG is mainly driven by IDL-C that includes cholesterol-rich remnants of fasting and postprandial lipoproteins (Rebolledo and Actis Dato 2005). Patients with atherosclerosis have postprandial hyperlipidaemia, even in the presence of normal fasting TG (Patsch et al. 1992). In postprandial hyperlipidaemia, the increased concentration of chylomicron and VLDL remnants seems to play an important role in inducing inflammation and oxidative stress in the bloodstream and at the endothelium via leucocytes and the complement system (Alipour et al. 2007). In addition, the prolonged catabolism of remnant lipoproteins leads to increased production of small, dense LDL, thereby further increasing the atherogenicity (Proctor and Mamo 1998; Alipour et al. 2007). Recent studies (Nordestgaard et al. 2007; Bansal et al. 2007) have further confirmed the role of non-fasting TG in cardiovascular events, suggesting that postprandial TG levels may be superior to fasting levels for assessment of CVD risk (Bansal et al. 2007).

Whether fasting TG is an independent predictor of CVD remains pending. Results from two meta-analysis studies, one consisting of 29 western European and North American prospective studies of 262 525 subjects (Sarwar et al. 2007) and another including 32 Asia Pacific cohort studies of 93 281 subjects (Barzi et al. 2005), showed that TG is associated with CHD risk with HRs (95%CI) of 1.72 (1.56-1.90) and 1.61 (1.39-1.86), respectively. Our study, along with some other European studies, did not reveal such an association in non-diabetic (Wang et al. 2007) or normoglycaemic subjects (Bos et al. 2003), whereas we do confirm the importance of TG in predicting CVD death in conditions quite similar to

manifest diabetes, like CH or newly diagnosed diabetes (Laakso 1996; Onat et al. 2006; Chan et al. 2005; Schulze et al. 2004).

This is the first study that has investigated the role of dyslipidaemia in predicting CVD mortality in subjects with isolated fasting or isolated post-load hyperglycaemia. In the present study, none of the lipid variables significantly predicted CVD mortality in the presence of isolated post-load hyperglycaemia. This adds up to many other different phenotypes (The DECODE Study Group 2003; The DECODE Study Group 2005; The DECODE Study Group 2001; Sorkin et al. 2005; Nakagami 2004) between IFG and IGT, i.e., age and gender difference in prevalence, less concordance between the two categories and difference in insulin resistance and secretion. The finding further suggests that, even though both IFG and IGT represent intermediate stages of glucose intolerance, they are likely to be distinct conditions with different pathophysiological etiologies. Future guidelines for lipid screening and CVD management in individuals with pre-diabetes or diabetes should consider these differences. Nevertheless, it should be borne in mind that the role of other lipid profiles which were not included in this data analysis such as postprandial lipaemia, apoB or small, dense LDL particles (Krauss 2004) is still not clear and needs further study.

#### **6.4 Lipids and lipoproteins and incidence of CHD by glucose categories**

To our knowledge, few studies have been published on the role of lipid parameters in predicting CHD in people with different glucose categories, i.e. IFG and/or IGT. Our study of Finnish and Swedish data with a median follow-up of 10 years (study V), showed that TC, HDL-C, non-HDL-C and TC/HDL-C were associated with risk for incident CHD not only in people with diabetes but also in those with normoglycaemia (NFG and NGT), independently of other analyzed risk factors. In addition, TC and non-HDL-C predicted CHD incidence in those with isolated IFG. In people with IGT or combined IFG and IGT, none of these lipid variables significantly predicted CHD risk. TG was not an independent predictor once non-HDL-C was taken into account, even in people with diabetes.

The association of lipids and lipoprotein patterns with CHD risk has been estimated in many epidemiological studies. Our findings supported by others (Laakso 1996; Boden 2000; Mora et al. 2008) showed that TC, HDL-C and non-HDL-C were similarly powerful risk factors for CHD in diabetic as in normoglycaemic individuals. Non-HDL-C, which includes all atherogenic lipoproteins, is also a CHD predictor, and may be superior to LDL-C for assessment of CVD risk (Pischon et al. 2005; Robinson et al. 2009). Previous studies have,

however, not included the glucose tolerance status in their analyses. It is possible that some of the effect associated with non-HDL-C is actually due to abnormal glucose tolerance. In contrast, the risk related to TG remains controversial in predicting CHD risk (Onat et al. 2006; Sarwar et al. 2007). The Hoorn study (Bos et al. 2003) showed an association of high TG with increased future CVD risk in people with abnormal glucose metabolism defined as having IFG, IGT, previously diagnosed or newly diagnosed diabetes, but non-HDL-C was not included in their analyses. Our finding that TG was an independent predictor in analyses including HDL-C but not in that with non-HDL-C is consistent with the fact that TG is a major constituent of VLDL and thus also part of non-HDL-C (Frost et al. 1996). The independent role of TG and CHD risk thus needs further investigation.

The current analysis of subjects free of CHD at baseline shows the lack of lipid-CHD association in people with post-load hyperglycaemia. This might be a chance finding or suggest a pathophysiological difference between IFG and IGT (Festa et al. 2004; Pankow et al. 2007; Nathan et al. 2007). Moreover, our knowledge regarding lipid-CVD association is again based on fasting measurements. Patients with atherosclerosis, however, often have increased postprandial hyperlipidaemia, even in the presence of normal fasting TG (Patsch et al. 1992). It is proposed that the postprandial rather than fasting measurement of TG might be a better indicator for CHD risk (Mora et al. 2008; McQueen et al. 2008). Increased production of TG-rich lipoproteins in the postprandial state may induce inflammatory changes and oxidative stress in the endothelial layer of the vessel walls (Proctor and Mamo 1998; Alipour et al. 2007), which may have rendered HDL dysfunction and impaired protection against CHD (Kontush and Chapman 2006). In addition, decreased HDL-C level (Branchi et al. 2006) and its glycoxidation impair the reverse cholesterol transport, providing an extra atherogenic mechanism (Rebolledo and Actis Dato 2005). In this population, HDL dysfunction may be less marked in diabetic subjects than in those with post-load hyperglycaemia (i.e., IGT), characterized by higher levels of remnant lipoproteins, oxidative stress and inflammation (Freiberg et al. 2008; Nordestgaard et al. 2007). In addition, increasing evidence shows that apoB/apoA-I may provide incremental value when traditional lipid variables are weakly predictive (Charlton-Menys et al. 2009; Ingelsson et al. 2007; Karthikeyan et al. 2009). This deserves further investigations.

## **6.5 Strengths and limitations of the study**

The study consisted of large populations of European and Asian origins and all studies were population-based with a random sampling approach except for the Hong Kong Workforce study (occupational study) and the Hisayama study (community-based study). Information

on CVD death or incident CHD events in both Finnish and Swedish cohorts has been obtained through national registers which have been approved to be valid and complete and uniformly classified according to the ICD coding. Populations of the same ethnicity were pooled to increase statistical power and “study cohort” was also considered as a covariate in the data analysis.

Although all blood samples for lipid assays were obtained in the fasting state (The DECODA Study Group 2007), a limitation of this study was the lack of standardization in assay methods for lipids in different laboratories. This needs to be kept in mind when interpreting or comparing the results for, in particular, HDL-C, the measurement of which remains a major challenge over time. Except for the direct assays applied in a few of the studies, most of the studies have used chemical precipitation methods for HDL-C assays, including the heparin/Mn<sup>2+</sup>, the dextran sulfate MgCl<sub>2</sub>, the phosphotungstate MgCl<sub>2</sub> and the polyethylene glycol method. The observed differences in HDL-C among ethnicities, to our knowledge, are less likely biased by the laboratory assays. Firstly, there is a good agreement and a similar accuracy between the results of most of the precipitation methods (Demacker et al. 1997). Secondly, the direct method and the precipitation method are shown to be closely correlated (Jensen et al. 2002). On average the HDL-C concentration obtained from the direct method is about 0.1-0.2 mmol/l higher than that from the precipitation method when TG is < 4.6 mmol/l (Jensen et al. 2002; Okazaki et al. 1997). The mean difference in the HDL-C concentration was about 0.4-0.5 mmol/l higher in Qingdao Chinese (direct or precipitation method) than in Asian Indians (precipitation method), much greater than that could be attributed to the difference in assay methods. Most importantly, our observation is consistent with previous reports regarding the adverse lipid profiles in Asian Indians compared with western or Chinese populations where the lipids were measured using the same assay procedure for Indians as for others (Mulukutla et al. 2008; Tan et al. 1999). Moreover the mean lipid levels in our study were similar to others. The mean TC was 4.4 mmol/l, HDL-C 1.03-1.04 mmol/l and TG 1.53-2.04 mmol/l for Asian Indians in the HeartSCORE and IndiaSCORE study (Mulukutla et al. 2008) and the Singapore National Health Survey (Tan et al. 1999). This further strengthens the validity of the study.

Due to the low number of incident CHD cases in women, sex-specific analysis could be done only in men but not in women. The results in study V seem to be conclusive for men and larger studies are required to confirm these findings in women. In addition, the absence of information on apoB and other lipoprotein subgroups limited the evaluation of novel atherogenic lipid parameters in relation to CHD risk.



## **6.6 Implications for current guidelines on CVD prevention and future research**

Regardless of the contribution of insulin resistance, IFG or IGT, as a clinical classification of intermediate hyperglycaemia, generally appeared to be associated with worse lipid profiles compared with normal glycaemia in our study. Increasing levels of glucose in the “high normal” range and the coexistence of other cardiovascular risk factors have been shown to be adversely associated with arterial endothelial dysfunction and intima-media thickening (Heiss et al. 1980). The cluster of hyperglycaemia and dyslipidaemia in non-diabetic population should be further emphasized in prevention of atherosclerosis and CVD. Current guidelines from the National Cholesterol Education Program Adult Treatment Panel III (Expert Panel 2001), the European Society of Cardiology (Graham et al. 2007) and the American Diabetes Association (American Diabetes Association 2010), mainly based on the data of whites, consistently recommend that LDL-C < 2.6 mmol/l should be the primary target of therapy in patients with diabetes. As shown in our study and others’ (Mulukutla et al. 2008; Karthikeyan et al. 2009), the Asian Indian population had significantly lower TC and LDL-C than did whites. The threshold of LDL-C for treatment target for Whites may be too high for Asian Indians. Further studies are warranted to verify this hypothesis and determine the threshold applicable to this ethnic group.

In contrast to LDL-C, HDL-C has been either dropped from (Graham et al. 2007) or set as a secondary (American Diabetes Association 2010) or tertiary (Expert Panel 2001) target in the major guidelines despite the strong evidence of reduced HDL-C as an independent risk factor for CVD (Boden 2000). This may change if more therapy choices developed to increase HDL-C levels and improve HDL function are shown to prevent CVD (Singh et al. 2007; Duffy and Rader 2009; Sorrentino et al. 2010) or reduce the residual cardiovascular risk (Fruchart J 2008). Most recently, the ARBITER 6-HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis) trial has shown a significant improvement in serum HDL-C levels and regression of carotid intima-media thickness when ERN was combined with statin therapy in patients with CHD or CHD equivalent (Taylor et al. 2009; Villines et al. 2010). Our study demonstrates distinct patterns of lipid profiles between different ethnic groups. Considering the high proportion of Asian Indians with adverse HDL-C levels, appropriate approaches to increasing HDL-C and/or improving HDL function may become an important treatment target in Asian Indians in order to reduce their excess CVD risks.

## 7 CONCLUSIONS

The findings and conclusions of original studies I to V can be summarized as follows:

- 1) Hyperglycaemia is associated with adverse lipid profiles in Europeans and Asians without a prior history of diabetes. Dyslipidaemia needs to be considered when assessing the risk of CVD in individuals with intermediate hyperglycaemia.
- 2) There are distinct patterns of lipid profiles associated with ethnicity regardless of the glucose levels, suggesting that ethnic-specific strategies and guidelines for CVD risk assessment and prevention are required.
- 3) Dyslipidaemia predicts CVD mortality or CHD incidence in either diabetic or non-diabetic individuals defined based on the fasting glucose criteria, but not on the 2-hour criteria. The difference between fasting and post-load hyperglycaemia with regard to the lipid-CVD relation may suggest different management strategies in people with fasting or post-load hyperglycaemia.

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# APPENDIX 1 Measures of lipid components in each study

Countries and studies	Blood sample	Total cholesterol	High-density lipoprotein cholesterol	Triglycerides
China				
Hong Kong Cardiovascular Disease Risk Factor Prevalence Study	Plasma	Cholesterol oxidase (CHOD) method; Hitachi 717 analyser (Hitachi Instruments, California, USA).	Measured after precipitation of very-low density lipoprotein (VLDL) and low-density lipoprotein (LDL) by polyethylene glycol PEG 6000.	Lipase/glycerol kinase method;
Hong Kong Workforce Survey on CVD Risk Factors	Venous Plasma	Enzymatic method, with reagents (Baker Instruments Corporation, Allentown, PA 18103, USA) with Cobas Mira analyzer (Hoffman-La Roche and Co., Basle Switzerland).	Enzymatic method after precipitation with dextran sulphate-MgCl <sub>2</sub> on Cobas Mira analyzer (Hoffman-La Roche and Co., Basle Switzerland)	Enzymatic method, with reagents (Baker Instruments Corporation, Allentown, PA 18103, USA) with Cobas Mira analyzer (Hoffman-La Roche and Co., Basle Switzerland)
Qingdao Diabetes Survey 2002	Venous Plasma	Enzymatic method (AMS Analyzer Medical System, SABA-18, Rome, Italy)	Enzymatic method after precipitation (AMS Analyzer Medical System, SABA-18, Rome, Italy)	Enzymatic method (AMS Analyzer Medical System, SABA-18, Rome, Italy)
Qingdao Diabetes Study 2006	Serum	Enzymatic method (Olympus reagent) With OLYMPUS-AU640 Automatic Analyzers (Olympus Optical. Tokyo, Japan)	Direct method (Olympus reagent) with OLYMPUS-AU640 Automatic Analyzers (Olympus Optical. Tokyo, Japan)	Enzymatic method (Olympus reagent) with OLYMPUS-AU640 Automatic Analyzers (Olympus Optical. Tokyo, Japan)
Finland				
East-West men	Serum	Enzymatic techniques (Monotest, Boehringer Mannheim GmbH, FRG)	Enzymetic method after precipitation of VLDL and LDL by	Enzymatic techniques (Monotest, Boehringer

		Olli C3000 photometer (Kone Oy, Finland)	means of dextran-magnesium-chloride, with Olli C3000 photometer (Kone Oy, Finland)	Mannheim GmbH, FRG)
National FINRISK Study 87, 92	Serum	Enzymatic techniques (Cholesterol oxidase-peroxidase-amidopyrine, CHOD-PAP, Boehringer-Mannheim, Mannheim, Germany)	Enzymatic method after dextran sulfate magnesium chloride precipitation of apolipoprotein B (apoB)-containing lipoproteins	Olli C3000 photometer (Kone Oy, Finland) Enzymatic techniques (CHOD-PAP, Boehringer-Mannheim, Mannheim, Germany)
National FINRISK Study 2002	Serum	Enzymatic method (CHOD-PAP; Thermo Elektron Oy, Finland);	Enzymatic method (CHOD-PAP; Thermo Elektron Oy, Finland) after precipitation by the PTA-precipitation method	Enzymatic techniques (Glycerol phosphate oxidase-peroxidase-amidopyrine, GPO-PAP; Thermo Elektron Oy)
Oulu Study	Serum	Enzymatic method (CHOD-PAP, Boehringer Mannheim, Mannheim, Germany).	Enzymatic CHOD-PAP method after precipitation of LDL and VLDL with a reagent containing phosphotungstic acid and MgCl <sub>2</sub> (Boehringer Mannheim)	Enzymatic method (CHOD-PAP, Boehringer Mannheim, Mannheim, Germany)
Savitaipale Study	Plasma	Enzymatic colorimetric method (CHOD-PAP) Cobas Integra 400/700 analyzer	Enzymatic colorimetric method (CHOD-PAP) Cobas Integra 400/700 analyzer	Enzymatic colorimetric method (CHOD-PAP) Cobas Integra 400/700 analyzer
Vantaa Study	Serum	Enzymatic techniques (Boehringer-Mannheim)	Enzymatic method after precipitation with polyethylenglycol	Enzymatic techniques (Boehringer-Mannheim)
India Chennai 94	Serum	Enzymatic method; Hitachi 704 autoanalyser, using Boehringer Mannheim (Mannheim, Germany) reagents	Phosphotungstate-magnesium precipitation method. Hitachi 704 autoanalyser, using Boehringer Mannheim (Mannheim,	Enzymatic method. Hitachi 704 autoanalyser, using Boehringer Mannheim (Mannheim, Germany)

Chennai 97	Venous Plasma	CHOD-PAP method (Boehringer Mannheim, Germany); Corning Express Plus Auto Analyser (Corning, medfied, MA, USA)	Germany) reagents Phosphotungstic acid method after precipitation of LDL and chylomicrons (Boehringer Mannheim, Germany); Corning Express Plus Auto Analyser (Corning, medfied, MA, USA)	reagents GPO-PAP method (Boehringer Mannheim, Germany); Corning Express Plus Auto Analyser (Corning, medfied, MA, USA)
CURES	Serum	CHOD-PAP method with Hitachi-912 Autoanalyser (Hitachi, Mannheim, Germany) using kits supplied by Roche Diagnostics (Mannheim, Germany).	Direct method (polyethylene glycol–pretreated enzymes) with Hitachi-912 Autoanalyser (Hitachi, Mannheim, Germany) using kits supplied by Roche Diagnostics (Mannheim, Germany).	GPO-PAP method; Hitachi-912 Autoanalyser (Hitachi, Mannheim, Germany) using kits supplied by Roche Diagnostics (Mannheim, Germany).
Chennai 2006	Serum	Standard enzymatic procedures (Roche Diagnostics, Mannheim, Germany)	Direct assay method (Roche Diagnostics, Mannheim, Germany)	Standard enzymatic procedures (Roche Diagnostics, Mannheim, Germany)
Italy Cremona Study	Plasma	Enzymatic techniques (Boehringer-Mannheim, Mannheim, Germany) with CIBA Corning 550 Express Auto-analyser	Precipitation with PEG using a Colortest kit (Roche, Basel, Switzerland).	Enzymatic techniques (Boehringer-Mannheim, Mannheim, Germany) with CIBA Corning 550 Express Auto-analyser
Japan Funagata Study	Plasma	Cholesterol oxidase method (L-type Wako CHO-H [Wako Pure Chemical Industries, Osaka, Japan])	Direct method (Cholesterol N HDL [Daiichi Pure Chemicals, Tokyo, Japan]) with TBA 80FR (Toshiba	GPO HDAOS method (Pureauto S TG-N [Daiichi Pure Chemicals, Tokyo,

		with TBA 80FR (Toshiba medical system corporation, Tokyo)	medical system corporation, Tokyo)	Japan]) with TBA 80FR (Toshiba medical system corporation, Tokyo)
Hisayama Study	Serum	Enzymatic techniques (TBA-80S; Toshiba Inc., Tokyo, Japan)	Enzymatic method after precipitation of of VLDL and LDL with dextran sulfate and magnesium (TBA-80S; Toshiba Inc., Tokyo, Japan)	Enzymatic techniques (TBA-80S; Toshiba Inc., Tokyo, Japan)
Mauritius Mauritius 1987	Venous plasma	Manual enzymatic colorimetric method (Coulter Minikem Spectrophotometer), (Boeringer Cat no 701912)	Manual enzymatic colorimetric method (Coulter Minikem Spectrophotometer), (Boeringer Cat no 701912)	Manual enzymatic colorimetric method(Coulter Minikem Spectrophotometer) (Boeringer Cat nr 400971)
Mauritius 1992	Venous plasma	Automated enzymatic method with Chemistry Profile Analyser Model LS (Coulter- France)	Precipitation method (Biomerieux) Automated enzymatic method, Chemistry Profile Analyser Model LS (Coulter- France)	Automated enzymatic method with Chemistry Profile Analyser Model LS (Coulter- France)
Mauritius 1998	Venous plasma	Automated enzymatic methods; Cobas Mira analyzer (Roche Diagnostics, France)	Precipitation method (Biomerieux) Automated enzymatic methods; Cobas Mira analyzer (Roche Diagnostics, France) Direct method (Biomerieux)	Automated enzymatic methods; Cobas Mira analyzer (Roche Diagnostics, France)
Poland POLMONICA	Serum	Direct Liebermann-Burchard method (Boehringer-Mannheim)	Determined in the supernatant after precipitation with heparin manganese (Boehringer-Mannheim)	Enzymatic method (Boehringer-Mannheim)
Republic of Cyprus				

Nicosia Diabetes Study Spain	Whole Blood	Cobas Micra Plus Roche	Cobas Micra Plus Roche	Cobas Micra Plus Roche
The Guía Study	Plasma	Standard enzymatic methods (Boehringer-Mannheim Hitachi 717 autoanalyser, Tokyo, Japan)	Phosphotungstate precipitation (Boehringer-Mannheim Hitachi 717 autoanalyser, Tokyo, Japan)	Standard enzymatic methods (Boehringer-Mannheim Hitachi 717 autoanalyser, Tokyo, Japan)
The Viva Study	Plasma	Enzymatic techniques (Boehringer- Mannheim)	Enzymatic techniques (Boehringer- Mannheim)	Enzymatic techniques (Boehringer-Mannheim)
Sweden MONICA	Serum	Enzymatic techniques (Boehringer- Mannheim GmbH, Germany)	Phosphotungstate-Mg <sup>2+</sup> precipitation method	Enzymatic method (CHOD- PAP, Boehringer-Mannheim GmbH, Germany)
The Uppsala Longitudinal Study of Adult Men (ULSAM)	Serum	Enzymatic techniques using IL Test Cholesterol Trinders's Method and IL Test Enzymatic-colorimetric Method for use in a Monarch apparatus (Instrumentation Laboratories, Lexington, USA). ( <a href="http://www.pubcare.uu.se/ULSAM/invest/70yrs/meth70.htm#09">http://www.pubcare.uu.se/ULSAM/ invest/70yrs/meth70.htm#09</a> )	Separated by precipitation with magnesium chloride/phosphotungstate.	Enzymatic techniques using IL Test Cholesterol Trinders's Method and IL Test Enzymatic-colorimetric Method for use in a Monarch apparatus (Instrumentation Laboratories, Lexington, USA).
The Netherlands The Hoorn Study	Serum	Enzymatic techniques (Boehringer- Mannheim, Mannheim, Germany);	Enzymatic techniques after precipitation of the low and very low-density lipoproteins (Boehringer-Mannheim, Mannheim, Germany)	Enzymatic techniques (Boehringer-Mannheim, Mannheim, Germany);
Zutphen	Serum	Enzymatic techniques (CHOD-PAP	Enzymatic method after	Enzymatic techniques (CHOD-

		mono-test kit, Boehringer-Mannheim)	precipitation of apoB-containing particles by means of dextran magnesium sulphate.	PAP mono-test kit, Boehringer-Mannheim)
U.K.				
Isle of ELY Diabetes Project	Plasma	Enzymatic techniques, RA 1000 (Bayer Diagnostics, Basingstoke, Hants, UK)	Enzymatic methods	Standard automated enzymatic method with the RA1000 (Bayer Diagnostics, Suffolk, U.K.),
Newcastle Heart Project	Plasma	Cholesterol oxidase/peroxidase method with Cobas Bio centrifugal analyzer (Roche Products Ltd, Welwyn Garden City, UK)	Measuring the supernatant cholesterol concentration after precipitation of apoB-containing lipoproteins with heparin and manganese. Cobas Bio centrifugal analyzer (Roche Products Ltd, Welwyn Garden City, UK)	Lipase/glycerol kinase method. Cobas Bio centrifugal analyzer (Roche Products Ltd, Welwyn Garden City, UK)
The Goodinge Study	Plasma	Cholesterol esterase method (Boehringer Mannheim, Lewes, Sussex, U.K.)	Enzymatic spectrophotometric method (Roche Diagnostics, Hatfield, Herts, U.K.) after precipitation of LDL by the addition of phosphotungstic acid in the presence of magnesium ions.	Enzymatic spectrophotometric method (Roche Diagnostics, Hatfield, Herts, U.K.).

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